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DEPARTMENT OF NEUROBIOLOGY, CARE SCIENCES AND  
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# **THE IMPACT OF DIABETES ON COGNITIVE AGING AND DEMENTIA**

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# The impact of diabetes on cognitive aging and dementia

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*Alla mia famiglia—To my family*

This is a corner of a larger field...

“Nothing in life is to be feared, it is only to be understood.  
Now is the time to understand more, so that we may fear less.”

*Marie Curie*



## ABSTRACT

The impact of prediabetes and diabetes on different stages of cognitive function during aging remains unclear. This thesis aimed to investigate the impact of prediabetes and of diabetes on cognitive aging—from cognitive deficits, through cognitive decline, to dementia—, explore underlying cerebral mechanisms and identify factors that may protect older adults with diabetes from dementia. The four studies in this thesis were based on data from the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), the SNAC-K brain magnetic resonance imaging (MRI) study, and the Swedish Adoption/Twin Study of Aging (SATSA).

**Study I.** This study used SNAC-K data to identify the cognitive domains sensitive to the detrimental impact of diabetes. In cognitively intact older adults, diabetes was associated with lower performance in perceptual speed ( $\beta$  -1.10; 95% CI -1.98, -0.23), category fluency ( $\beta$  -1.27; 95% CI -2.52, -0.03), and digit span forward ( $\beta$  -0.35; 95% CI -0.54, -0.17). These results suggest that domains of fluid abilities are more sensitive to diabetes than are other cognitive domains.

**Study II.** This study used 23 years of follow-up data from SATSA to investigate the effect of prediabetes and of diabetes on trajectories of cognitive decline in different domains. Diabetes accelerated cognitive decline in perceptual speed ( $\beta$  -0.25; 95% CI -0.44, -0.05) and verbal abilities ( $\beta$  -0.19; 95% CI -0.33, -0.04). Prediabetes was associated with poor memory performance at baseline but with a less steep memory decline over time.

**Study III.** The relationship of prediabetes and of diabetes with global cognitive decline and structural brain changes was assessed with data from SNAC-K and the SNAC-K MRI study. Both accelerated global cognitive decline. Prediabetes was associated with smaller global brain volume, particularly smaller white matter volume at baseline, and diabetes with accumulation of white matter hyperintensities ( $\beta$  0.56, 95% CI 0.07–1.05) over time.

**Study IV.** The compensatory effect of an active and socially integrated lifestyle on dementia risk in older adults with diabetes was examined with data from SNAC-K. Participants with diabetes and an inactive lifestyle had a higher risk of dementia (HR 6.0, 95% CI 3.0–12.3) than diabetes-free participants with an active lifestyle (high engagement in leisure activities or/and rich social network). In participants with diabetes, an active lifestyle was associated with less of a raised risk (HR 1.9, 95% CI 1.1–3.4).

**Conclusions.** In the initial phase of cognitive deterioration, the domains primarily affected by diabetes may be processing speed, executive function, and attention/primary memory. Over time, having either prediabetes or diabetes accelerates the decline in fluid abilities (i.e., perceptual speed and verbal abilities) and global cognitive decline. At the structural brain level, diabetes is associated with the accumulation of cerebral microvascular lesions, which might start already during prediabetes. Finally, diabetes is associated with an increased risk of dementia. However, an active and socially integrated lifestyle may significantly counteract the detrimental effect of diabetes on brain aging.

**Key words:** prediabetes, type 2 diabetes, cognitive domains, cognitive decline, dementia, neuroimaging, white matter hyperintensities, cohort study, active lifestyle

# SAMMANFATTNING

Påverkan av diabetes och prediabetes på olika stadier av kognitivt fungerande under åldrandeprocessen är ännu inte klarlagt. Syftet med denna avhandling var att undersöka hur diabetes och prediabetes påverkar kognitiv svikt, från begynnande kognitiv försämring till demens i en åldrande befolkning. Utöver det undersöks de underliggande hjärnmekanismerna och möjliga kompensatoriska faktorer mot demens för individer med diabetes. Avhandlingen innehåller fyra separata studier som använder data från "the Swedish National Study on Aging and Care-Kungsholmen" (SNAC-K), "SNAC-K brain magnetic resonance imaging" (MRI) studien, och "the Swedish Adoption/Twin Study of Aging" (SATSA). De viktigaste resultaten är:

**Studie I.** Vi identifierade samband mellan diabetes och olika kognitiva domäner med hjälp av data från SNAC-K. Bland de med normal kognitiv förmåga fann vi samband mellan diabetes och lägre perceptuell snabbhet ( $\beta$  -1.10; 95% CI -1.98, -0.23), verbalt flöde ( $\beta$  -1.27; 95% CI -2.52, -0.03), och uppmärksamhet ( $\beta$  -0.35; 95% CI -0.54, -0.17). Resultaten tyder på att diabetes påverkar flytande kognitiva förmågor tidigare än andra domäner.

**Studie II.** Med hjälp av SATSA undersökte vi effekten av diabetes och prediabetes på den kognitiva försämringstakten i olika kognitiva domäner under 23 år. Diabetes ökade den kognitiva försämringstakten inom perceptuell snabbhet ( $\beta$  -0.25; 95% CI -0.44, -0.05) och verbala förmågor ( $\beta$  -0.19; 95% CI -0.33, -0.04). Prediabetes hade ett samband med sämre minne vid första undersökningstillfället men också med en långsammare försämring av minnesförmåga över tid.

**Studie III.** Sambandet mellan diabetes, prediabetes och kognitiv försämringstakt samt strukturella hjärnförändringar undersöktes i SNAC-K och SNAC-K MRI. Prediabetes och diabetes påskyndade den kognitiva försämringen. Prediabetes hade ett samband med mindre hjärnvolym, speciellt den vita hjärnsubstansen, vid första undersökningstillfället. Diabetes var kopplat till ackumulation av vitsubstansskador över tid ( $\beta$  0.56, 95% CI 0.07–1.05).

**Studie IV.** Med data från SNAC-K undersöktes positiva effekter av en aktiv (t.ex. högt deltagande i fritidsaktiviteter) och social livsstil (t.ex. ett stort nätverk) på sambandet mellan diabetes och demens. Personer med diabetes och en inaktiv livsstil hade högre risk för demens än personer fria från diabetes med en aktiv livsstil (HR 6.0, 95% CI 3.0–12.3). Personer med diabetes med en aktiv livsstil hade inte en lika stor risk för demens (HR 1.9, 95% CI 1.1–3.4)

**Sammanfattning.** Perceptuell snabbhet, exekutiv förmåga och uppmärksamhet kan vara de första domänerna som påverkas av diabetes under den kognitiva försämringen. Prediabetes och diabetes kan påverka flytande kognitiva förmågor (tex perceptuell snabbhet och verbalt flöde) och globala kognition negativt över tid. Diabetes, och eventuellt även prediabetes, har ett samband med ökat antal mikrovaskulära skador i hjärnan. Avslutningsvis ökar diabetes risken för demens men en aktiv och social livsstil kan motverka de negativa effekterna av diabetes på hjärnans åldrande.

**Nyckelord:** prediabetes; typ 2 diabetes; kognitiva domäner; kognitiv försämringstakt; demens; hjärnavbildning; vitsubstansskador; kohortstudie; aktiv livsstil.



## RIASSUNTO

L'impatto del diabete e prediabete sulle diverse fasi del funzionamento cognitivo durante l'invecchiamento rimane poco chiaro. Questa tesi ha indagato l'impatto del prediabete e del diabete sull'invecchiamento cognitivo—dai deficit cognitivi, attraverso il declino cognitivo, fino alla demenza—esplorandone i meccanismi cerebrali, e ha identificato i fattori che potrebbero proteggere gli anziani con diabete dalla demenza. I quattro studi presentati in questa tesi utilizzano dati dai seguenti database: Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), SNAC-K brain magnetic resonance imaging (MRI) e Swedish Adoption/Twin Study of Aging (SATSA).

**Studio I.** Questo studio ha utilizzato i dati di SNAC-K per identificare i domini cognitivi più sensibili all'impatto dannoso del diabete. Negli anziani cognitivamente intatti, il diabete è associato a minore velocità psicomotoria ( $\beta$  -1.10; 95% CI -1.98, -0.23) e scarse performance nella fluenza verbale per categorie ( $\beta$  -1.27; 95% CI -2.52, -0.03) e nello span di cifre in avanti ( $\beta$  -0.35; 95% CI -0.54, -0.17). Questi risultati suggeriscono che i domini delle abilità fluide sono più sensibili ai danni legati al diabete rispetto agli altri domini cognitivi.

**Studio II.** Questo studio ha utilizzato i dati di 23 anni di follow-up di SATSA per investigare l'effetto del prediabete e diabete sulle traiettorie di declino cognitivo in diversi domini. Il diabete è associato a un maggiore declino nella velocità psicomotoria ( $\beta$  -0.25; 95% CI -0.44, -0.05) e nelle abilità verbali ( $\beta$  -0.19; 95% CI -0.33, -0.04). Il prediabete è associato a scarse prestazioni di memoria al basale, ma con minore declino mnemonico nel tempo.

**Studio III.** La relazione tra prediabete, diabete, declino cognitivo globale e cambiamenti cerebrali strutturali è stata valutata utilizzando dati di SNAC-K e SNAC-K MRI. Prediabete e diabete mostrano un declino cognitivo globale accelerato. Durante il follow-up, il prediabete è associato con minore volume cerebrale, in particolare della sostanza bianca, mentre il diabete è associato con un accumulo più veloce di iperintensità della sostanza bianca cerebrale.

**Studio IV.** L'effetto compensatorio di uno stile di vita attivo e socialmente integrato sul rischio di demenza nel diabete è stato esaminato usando i dati di SNAC-K. I partecipanti con diabete e stile di vita inattivo hanno un aumentato rischio di demenza (HR 6.0, 95% CI 3.0-12.3) rispetto agli anziani non-diabetici con stile di vita attivo (elevato coinvolgimento in attività ricreative e/o ricca rete sociale). Nei partecipanti con diabete, uno stile di vita attivo è associato a un minor rischio di demenza (HR 1.9, IC 95% 1.1-3.4).

**Conclusione.** Nella fase iniziale del deterioramento cognitivo, i domini primariamente danneggiati dal diabete sono velocità psicomotoria, le funzioni esecutive, e attenzione/memoria primaria. Le persone con prediabete o il diabete hanno un accelerato declino cognitivo delle abilità fluide (ad esempio, la velocità psicomotoria e le abilità verbali) e declino cognitivo globale. A livello cerebrale, il diabete si associa ad un accumulo di lesioni cerebrali microvascolari, che potrebbero iniziare già durante la fase prediabetica. Infine, il diabete aumenta il rischio di demenza. Tuttavia, uno stile di vita attivo e socialmente integrato può contrastare in modo significativo l'effetto dannoso del diabete sull'invecchiamento cerebrale.

**Parole chiave:** prediabete; diabete di tipo 2; domini cognitivi; declino cognitivo; demenza; neuroimmagine; iperintensità della sostanza bianca; studio di coorte; stile di vita attivo.

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- IV. **Marseglia A**, Wang HX, Rizzuto D, Fratiglioni L, Xu W. An active lifestyle and a rich social network counteract the risk of dementia related to diabetes: a population-based cohort study—*Submitted*

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## LIST OF ABBREVIATIONS

AD	Alzheimer's disease
<i>APOE</i> $\epsilon$ 4	Apolipoprotein E gene- $\epsilon$ 4 allele
BBB	Blood-brain barrier
BMI	Body mass index
CI	Confidence intervals
CIND	Cognitive impairment-no dementia
CVDs	Cardio- and cerebrovascular disorders
FBG	Fasting blood glucose
GMV	Grey matter volume
HbA1c	Glycated hemoglobin
HR	Hazard ratios
HV	Hippocampal volume
ICD-10	International Classification of Disease-tenth revision
IFCC	International Federation of Clinical Chemistry
IPT	In-person testing
IR	Incidence rates
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NGSP	National Glycohemoglobin Standardization Program
RBG	Random blood glucose
SATSA	Swedish Adoption/Twin Study of Aging
SD	Standard deviation
SNAC-K	Swedish National Study on Aging and Care-Kungsholmen
SVD	Small vessels diseases
TBTV	Total brain tissue volume
TIV	Total intracranial volume
VaD	Vascular dementia
VRF	Vascular risk factors
WAIS	Wechsler Adult Intelligence Scale
WMH(V)	White matter hyperintensities (volume)
WMV	White matter volume





# 1 INTRODUCTION

## 1.1 AGING—THE BURDEN OF DIABETES AND DEMENTIA

Decreasing mortality in people of all ages has contributed to an increase in life expectancy, which is a key driver of the world's rapidly growing aging population (1). Increasing life expectancy is a success story, as it reflects better living conditions, and especially after the 50s, improved health care and public health. However, with increasing age, several pathological changes occur in the body, affecting all organs. Consequently, as the population ages, a substantial increase in numbers of chronic and neurodegenerative disorders, such as dementia, is expected.

Dementia is a syndrome caused by a range of neurological conditions and characterized by progressive functional impairment of mental processes (also known as cognitive domains), such as memory, attention, speed of processing information, executive function, reasoning, visuospatial abilities, and language (2, 3). Dementia is a huge burden for patients, their families, and society, as by definition, the cognitive deficits interfere with daily personal, social, and professional life. Dementia's consequences are devastating both at the individual and societal level (3). In 2015, almost 47 million people aged  $\geq 60$  years, a number that corresponds to 5% to 7% of the worldwide population, had dementia; these numbers are expected to nearly triple in the next 30 years (3, 4). Alzheimer's disease (AD) is the most common cause of dementia in older adults, accounting for 50% to 70% of cases. Next most common are vascular dementia (VaD) and mixed dementia (3). Dementia begins several years before its clinical diagnosis (5), and several studies suggest that cognitive deficits in different domains can be detected nearly a decade before the diagnosis (6). Type 2 diabetes (hereafter, diabetes) has been identified as one of the major risk factor for dementia, conferring about double the risk (7, 8). A 2014 study estimated that almost 3% of dementia cases can be attributed to diabetes (9).

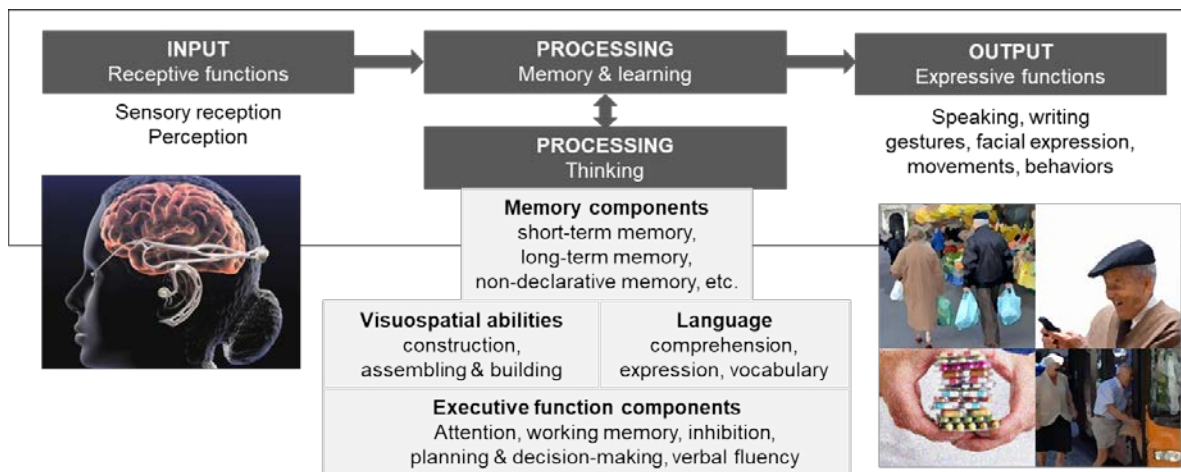
Briefly, diabetes is a chronic metabolic condition characterized by increased levels of glucose in the blood, i.e. hyperglycemia. It occurs when the pancreas cannot produce any or enough insulin or the body cannot effectively use the produced insulin (10). Diabetes is one of the leading causes of cardio- and cerebrovascular disorders, retinopathy, disability, and death and it imposes a significant economic burden on healthcare systems (11). According to the latest report from the International Diabetes Federation, in 2017, there were 123 million people aged 65 years or older living with diabetes in the world (9.6% of the population older than 65 years), including 29 million in Europe (11). Prediabetes is a highly heterogeneous metabolic state characterized by hyperglycemia, but at concentration below that required for diabetes diagnosis. It usually precedes diabetes. Overall, prediabetes affects 352 million adults in the world (7.3% of the adult population), and up to 10% of prediabetes cases will progress to diabetes every year (12).

Diabetes and dementia have emerged as major global health issues and burdens in people older than 60 years. Both the aging global population and less healthy lifestyles are

contributing to the rapid increase in the numbers of older people with diabetes and/or dementia. The numbers of older people with diabetes or dementia are foreseen to rise substantially in the next three decades—from 123 million to 253 million for diabetes, and from 47 million to 132 million for dementia (4, 11). Currently, there is no pharmacological treatment to cure dementia, and preventative strategies that target potential causes or mediators are still under debate. With this in mind, diabetes and prediabetes should be regarded as important targets for the prevention of dementia syndromes (8).

## **1.2 PREDIABETES, DIABETES, AND COGNITIVE AGING**

Cognitive aging has been defined as the “lifelong process of gradual, ongoing, yet highly variable changes in cognitive function that occurs when people get older” (13). Age-related physiological changes also affect the brain, both its physical structures and its ability to execute various functions (i.e., cognitive function). Therefore, as people age, their cognitive function gradually starts to decline. The decline shows great inter- and intra-individual variability across different domains (e.g., memory, attention, processing speed, and executive function) (13). People need preserved cognition to function well in daily life (e.g., solve problems, manage finances, handle medications, and keep house), perform basic activities of daily living (such as feeding, dressing, and toileting), engage in an active lifestyle, maintain social interactions, and therefore age successfully. The brain-computer metaphor (illustrated in detail in **Figure 1**) can be used to better understand how brain and cognition are related to functioning in everyday life (2). In brief, the sensory organs’ receptors receive environmental information (analogous to a computer receiving input), which is transduced to an action potential and conducted to specific brain areas where the stimuli are actively processed. The perceived information can either be consolidated and stored in long-term memory for future retrieval or temporarily stored in short-term memory and carried into other brain areas related to specific cognitive domains where the information is further reorganized and processed (analogous to a computer's processing phase). The elaborated information is, finally, retrieved and conveyed to a specific system (such as the motor cortex) that will produce a behavioral response (analogous to a computer's output) (2).



**Figure 1. The relationship between brain receptive functions, brain cognitive processes, and daily life behaviors is analogous to the relationship between computer input, processing, and output.**

However, as people age, multiple health-related conditions such as cerebro- and cardiovascular disorders (CVDs), metabolic disorders, and neurodegenerative disorders can affect cognitive function, accelerating cognitive aging (14). Cognitive impairment is an intermediate stage between expected age-related cognitive changes and disease-related cognitive changes and as such will likely evolve to dementia over time (15). Identifying cognitive profiles associated with age-related health conditions (i.e., prediabetes or diabetes) is important because such profiles can improve our understanding of 1) the nature of the association between the specific health condition and the related cognitive decline and 2) the underlying biological mechanisms, thereby helping prevent cognitive impairment and dementia in old age.

### 1.2.1 Prediabetes, diabetes, and deficits in cognitive domains

As early as the 1920s, researchers recognized that diabetes may affect cognitive function (16). Since then, numerous studies have examined the association between diabetes and cognitive function. We identified 30 *cross-sectional or case-control* studies that have addressed this topic in the last two decades; the methods and findings of these studies are summarized in Appendix 11.1. These studies consistently showed that older people with diabetes have modestly worse cognition than those who are diabetes-free. However, the cognitive domains affected by diabetes are less clear. The relationships between diabetes and the cognitive domains of memory (i.e., episodic, semantic, primary, and working memory), attention/executive function, and processing speed are the most studied, and results have been mixed. Twenty-five studies have examined the relationship between memory function and diabetes. Only nine studies reported significant associations between diabetes and poor memory performance (17-25), whereas the remaining studies found no association (26-41). Attention/executive function was considered in 20 studies, of which 13 reported significantly lower performance in people who had diabetes than those who did not (17, 21, 23, 27-33, 38,

41, 42). An association between deficits in processing speed and diabetes has been observed in some studies (17, 21-23, 29, 31-33, 36, 42), but not in others (18, 19, 25, 34, 40).

Visuospatial and language domains have been less explored, and findings on their association with diabetes differed. Two out of the eight studies found lower performance on visuospatial tasks that require spatial and constructional skills in people with diabetes than in people without the disease (23, 28). Similarly, of the 10 studies that examined verbal fluency, only two reported poorer performance in people with diabetes than people without diabetes (24, 38). Few studies have examined the relationship between prediabetes and cognitive deficits, and they reported no association (17, 27, 31, 36, 39). Altogether, these findings suggest that memory, executive function, and speed might be impaired in people with diabetes, but not in those with prediabetes.

Discrepancies among these studies may reflect methodological differences in the number and characteristics of study participants and the assessments of both diabetes and cognitive domains. First, about half of these studies assessed diabetes based on self-report or use of antidiabetic medications without including any measures of blood glucose, and they did not consider prediabetes. Second, important confounders (e.g., age, education, comorbidities) and potential effect modifiers varied across the studies. Third, many studies included screening test for global cognition (i.e., the Mini-Mental State Examination or MMSE). This would increase ceiling and floor effects and not capture subtle cognitive deficits, particularly in speed and executive function. Moreover, most studies have used only one test to assess each cognitive domain that would increase the measurement error, thus increasing error variance. Fourth, participants with dementia (which was usually assessed via self-report), were excluded in only half of the studies and none of these previous studies took cognitive impairment into account. People with cognitive impairment or dementia were thus included, so the observed cognitive deficits may reflect underlying neurodegenerative pathology rather than a specific diabetes-related etiology.

### **1.2.2 Prediabetes, diabetes, and cognitive decline**

We identified 28 *longitudinal* studies that examined the relationship between diabetes and cognitive decline (Appendix 11.2). Although some studies found accelerated cognitive decline in older people with diabetes (43, 44), others did not observe such an association (26, 29, 33, 36, 45-47). Furthermore, findings on the cognitive domains affected by diabetes were inconsistent. Only five studies addressed the effect of prediabetes on the rate of cognitive decline (27, 36, 41, 48, 49); they reported no association.

Fourteen studies included people aged  $\geq 60$  years; three of these included people  $\geq 75$  years (26, 33, 50), and 13 included participants  $\geq 40$  years. Follow-up varied between one and 20 years; however, only six studies had relatively long follow-up periods ( $\geq 10$  years) (27, 45, 51-54). Additionally, the majority of the studies examined diabetes as predictor of cognitive decline without specifying the stage of cognitive aging that was of interest; i.e., overall

decline or decline prior to dementia. Consequently, the inclusion of cognitive impairment or incident dementia cases together with the wide age ranges might have led to reverse causation or systematic errors. The studies assessed cognitive domains differently. They most often used screening tools such as the MMSE or single cognitive tests to evaluate cognitive domains. Only nine studies have used composite measures derived from a battery of cognitive tests (12, 27, 29, 46, 49, 52, 55-57); of those, one study extracted the domains with factor analysis (58). The use of composite domain measures reduces the complexity of data and the likelihood of measurement errors (e.g., floor and ceiling effects) that distort estimates of change. Furthermore, error variance associated with specific cognitive tasks is minimized when composite domains are extracted by structural equation modeling or factorial analyses. Finally, in previous studies, the ascertainment of diabetes was heterogeneous. Diagnostic tests for diabetes such as oral glucose tolerance, glycated hemoglobin (HbA1c), random blood glucose (RBG), or fasting blood glucose (FBG) were used in half of the studies. The other half assessed diabetes via self-reported diabetes or self-reported use of glucose-lowering medications, which can lead to misclassification and underdiagnosis of diabetes and prediabetes.

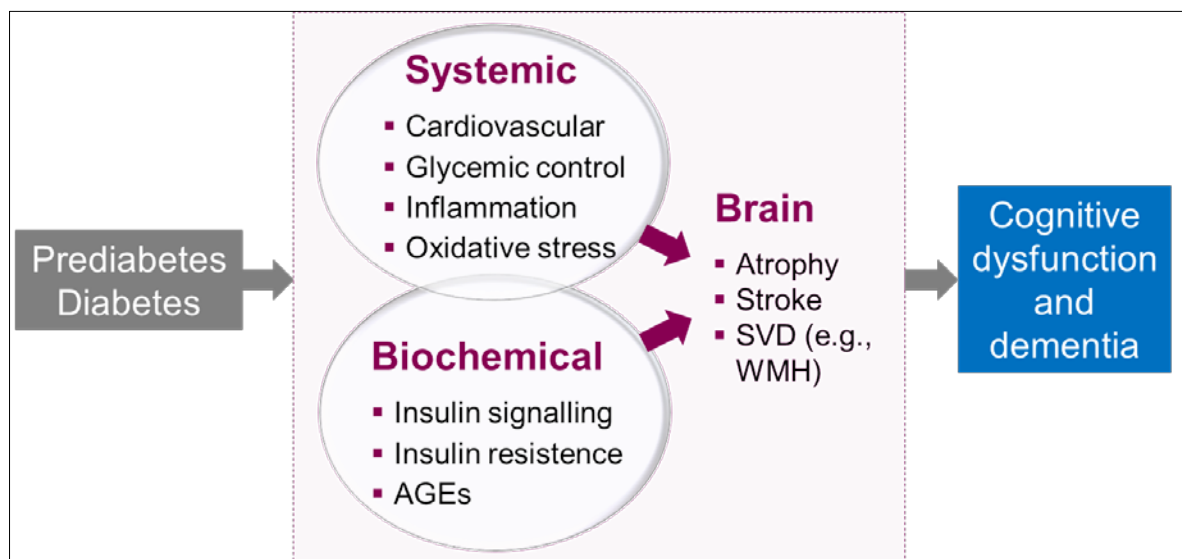
### **1.2.3 Prediabetes, diabetes, and dementia**

Diabetes is a well-established risk factor for dementia. It confers an approximately 60% increase in the risk of all-cause dementia, a 40% increase in the risk of non-vascular dementia, and up to 2.3-times higher risk of vascular dementia (8, 59). However, it is not clear whether prediabetes predicts dementia and studies addressing this question are relatively sparse. A study using data from the Kungsholmen project was the first to show that prediabetes was associated with a 70% increased risk of dementia (60). Since then, few prospective studies have explored the link between different markers of prediabetes—impaired glucose tolerance (IGT), FBG, or insulin resistance—and dementia, and the results of the studies that have been done are controversial. Findings from a 15-year follow-up study in Sweden showed that women with impaired FBG had higher odds of dementia than women with normal blood glucose (61). However, another Swedish community-based study that included >70-year-old men reported no association between FBG or impaired glucose tolerance and dementia over 12 years of follow-up (62). Discrepancies in findings may reflect differences in the laboratory tests used to identify prediabetes and in the tests used to assess dementia, which were mostly screening tools, rather than clinical assessments.

## **1.3 PREDIABETES, DIABETES, AND BRAIN AGING**

The biological bases that underpin the relationship between prediabetes or diabetes and cognitive aging are still unclear. Researchers have proposed that the pathogenesis is multifactorial, involving a complex interplay between systemic, biochemical, and cerebral mechanisms (63-65) (**Figure 2**).

Brain atrophy is the most investigated cerebral marker of diabetes-related cognitive decline and dementia (5). It is characterized by widened sulci, narrowed gyri, thinning of the cortical mantle, and consequent reduction of brain tissue size (so-called shrinkage) due to the progressive loss of neurons and their connections (2). As aging advances, the brain slowly undergoes some modifications, and neuronal loss occurs naturally as a defensive mechanism when cells are damaged (2). However, neurodegenerative diseases are characterized by excessive apoptosis and subsequent progressive brain atrophy (5, 66). Metabolic conditions and hyperglycemia affect the vascular system by accelerating atherosclerotic processes in the brain, results in brain abnormalities such as white matter loss and brain atrophy (2, 67, 68). The medial temporal lobe contains structures, such as the hippocampus and adjacent regions, that are essential for episodic memory and long-term memory (69). Medial temporal lobe atrophy is a core feature of typical AD (70). On the other hand, small vessels disease (SVD), including brain atrophy and white matter hyperintensities (WMH), are the major contributors to vascular dementia (71). Currently, two plausible pathways have been hypothesized to explain the association between diabetes and accelerated cognitive decline/dementia: 1) AD-related neurodegeneration (i.e., medial temporal lobe atrophy [including hippocampal atrophy]), and 2) cerebrovascular-related lesions (65).



**Figure 2. Multifactorial pathways underlying cognitive dysfunction and dementia in people with diabetes.**

The biological mechanisms of prediabetes- and diabetes-related cognitive dysfunction or dementia rely on a complex interplay between several mechanisms that probably stem from hyperglycemia. Cardiovascular diseases, chronic inflammation, high glucose levels, and advanced glycoxidation end-products (AGEs) can accelerate atherosclerotic processes in the brain, resulting in brain abnormalities; that is, atrophy and small vessel diseases (SVD), including white matter hyperintensities (WMH). These brain abnormalities may accelerate cognitive decline and, over time, lead to dementia.

In the last twenty years, brain-imaging techniques have greatly advanced our clinical and scientific understanding of the etiology of different dementia syndromes. Magnetic resonance imaging (MRI) is an excellent technique at detecting structural brain markers of AD- or cerebrovascular-related degeneration (72, 73). Previous cross-sectional studies have consistently shown associations between diabetes and smaller total brain volume (63, 74-79). We identified only six longitudinal studies from the last 20 years that have used structural MRI to address the effects of diabetes on brain atrophy (Appendix 11.3) (80-85). Some reported faster rates of brain volume loss, especially in the lateral ventricles, in people with diabetes than in those without the disease (80-82, 85). However, other studies did not find differences in the rate of brain volume loss between people with and without diabetes (83, 84). These longitudinal studies differ in the methods used to measure brain atrophy (thickness-based vs. volume-based) and the markers of brain atrophy itself (e.g., total brain tissue and gray matter, white matter, and ventricular volumes), which could explain the heterogeneous results.

Recently, there has been increasing interest in understanding the extent to which SVD contribute to diabetes-related cognitive dysfunction and dementia. SVD are a group of pathological processes with various etiologies that affect the small arteries, arterioles, venules, and capillaries of the brain (86). During aging, SVD are one of the major contributors to vascular cognitive impairment and dementia (71). Signs of SVD include small subcortical infarcts, lacunes, microbleeds, perivascular spaces, brain atrophy, and WMH (71). WMH are patchy or confluent hyperintensities in the white matter detected on the MRI that are linked to demyelination and axonal destruction (i.e., extensive WMH) or microglia and endothelial activation (i.e., subtle WMH) (87, 88). Diabetes has been associated with higher burden of SVD (63). In particular, its association with WMH has been investigated in several studies, but results are inconsistent. A few cross-sectional studies found greater WMH volume or more white matter lesions in older adults with diabetes than in those without diabetes (74, 76, 89), but most reported no differences (77, 79, 90, 91). To our knowledge, only four longitudinal studies have examined whether diabetes is related to WMH changes; they report no differences in the rates of change between people with and without diabetes (81-83, 85).

Because of the established association between diabetes and AD, numerous researchers have investigated whether diabetes is associated with structural abnormalities in the hippocampus; results are mixed. Only two cross-sectional studies found that lower hippocampal volumes were related to diabetes (77, 79), whereas longitudinal studies found no associations (63, 83).

Finally, three cross-sectional (74, 76, 89) and two longitudinal (80, 83) population-based studies examined the relationship between prediabetes and structural brain MRI markers. They reported mixed results.

## 1.4 KNOWLEDGE GAPS

Taken together, the findings of previous studies highlight important gaps in knowledge regarding prediabetes or diabetes and cognitive aging.

First, the initial phases of cognitive deterioration related to diabetes remain insufficiently explored, and the cognitive domains affected early by diabetes have not yet been characterized. Second, whether diabetes and especially prediabetes are associated with cognitive decline remains unclear. Third, the biological mechanisms underlying cognitive decline in diabetes remain unclear. In particular, it is not clear whether cognitive dysfunction is linked to vascular or AD-related neurodegenerative mechanisms. Furthermore, we do not know whether already prediabetes affects the brain, and there is a lack of population-based MRI studies on the association between prediabetes and brain markers of AD-related or vascular degeneration. Similarly, although the relationship between diabetes and dementia is well established, much less is known about the association between prediabetes and increased risk of dementia.

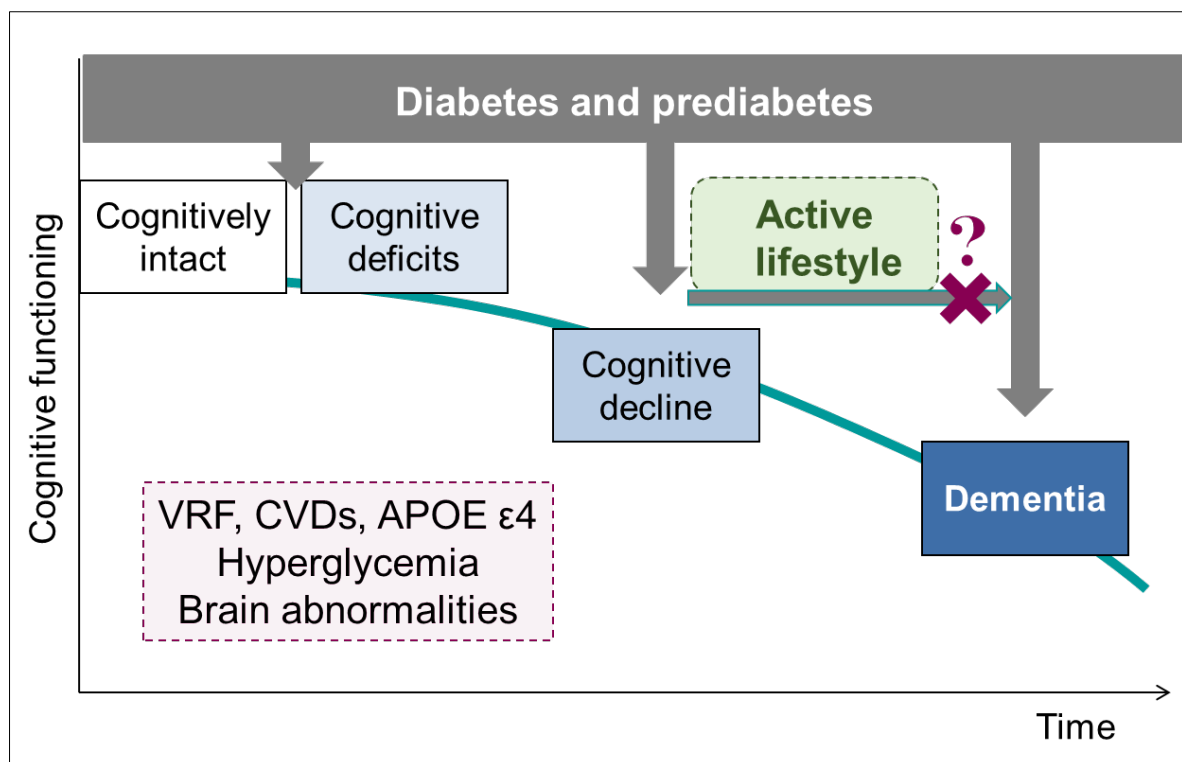
Finally, numerous studies have tried to understand the individual risk factors that can predict an increased risk of diabetes or an increased risk of dementia. However, none has tried to understand which protective modifiable lifestyle behaviors can protect people with diabetes from dementia. Indeed, as dementia and diabetes share similar risk factors, mostly related to lifestyle behaviors (92, 93), it seems reasonable to hypothesize that an active lifestyle could lower the risk of dementia in people with diabetes.



## 1.5 RESEARCH HYPOTHESIS

This thesis tested the hypothesis that prediabetes and diabetes affect different phases of cognitive aging. In cognitive aging, a person can move from being cognitively intact, to experiencing the onset of slight cognitive deficits, through cognitive decline, to dementia.

An underlying assumption in the thesis was that high blood glucose (i.e., hyperglycemia), CVDs, vascular risk factors (VRF), and *APOE*  $\epsilon 4$  may modulate the relationship between prediabetes or diabetes and accelerated cognitive aging. A second underlying assumption was that brain markers such as atrophy and microvascular lesions could explain this relationship. A third was that other modifiable factors, such as an active lifestyle, could help slow prediabetes- or diabetes-related cognitive aging (**Figure 3**).



**Figure 3. Schematic representation of the research hypothesis.**

Abbreviations: *APOE*  $\epsilon 4$ , apolipoprotein E gene- $\epsilon 4$  allele; CVDs, cardio- and cerebrovascular disorders; VRF, vascular risk factors.



## 2 AIMS

### 2.1 GENERAL AIM

This thesis investigated the impact of prediabetes and diabetes on different phases of cognitive aging (from being cognitively intact, through experiencing cognitive decline, to dementia), exploring the cerebral mechanisms that underlie the impact of prediabetes and diabetes on cognitive decline and attempting to identify factors that may protect people with diabetes from dementia.

### 2.2 SPECIFIC AIMS

The specific aims addressed in four studies were:

1. To identify which cognitive domains are impaired early by prediabetes and diabetes and, to explore whether glycemic control, VRFs, CVDs, and *APOE*  $\epsilon$ 4 modulate the association between prediabetes or diabetes and cognitive function (*Study I*).
2. To examine the long-term effect of prediabetes and diabetes on trajectories of cognitive decline in different domains prior to the diagnosis of dementia (*Study II*).
3. To investigate the impact of prediabetes and diabetes on global cognitive decline and brain structural changes (*Study III*).
4. To estimate the relationship between prediabetes and dementia and diabetes and dementia, and to explore whether an active lifestyle could counteract the risk effect of prediabetes or diabetes on dementia (*Study IV*).



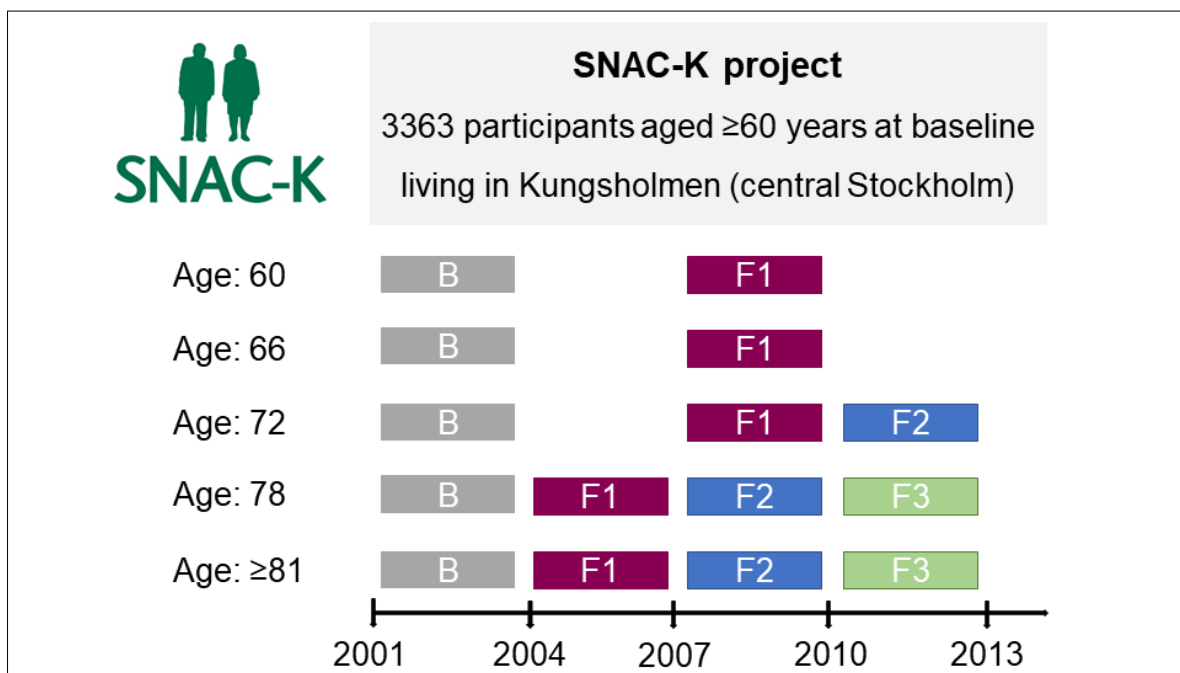
### 3 MATERIALS AND METHODS

This PhD project is based on data from the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), the SNAC-K brain MRI study (SNAC-K MRI), and the Swedish Adoption/Twin Study of Aging (SATSA).

#### 3.1 POPULATION-BASED DATASETS

##### 3.1.1 The Swedish National Study on Aging and Care-Kungsholmen

During March 2001 through June 2004, 4790 eligible people, aged  $\geq 60$  years, living either at home or in institutions in Kungsholmen (central Stockholm, Sweden) were invited to participate in the baseline assessment. The sampling was stratified by eleven specific age-cohorts and assessment interval (i.e. three and six years) because of more rapid changes in health and a higher attrition rate in older age groups. The younger age cohorts (60, 66, and 72 years) were followed every sixth year and the older age cohorts (78, 81, 84, 87, 90, 93, 96, and  $\geq 99$  years) every third year (**Figure 4**). Of the original 5111 people invited to participate, 262 had no contact information, 200 died before the baseline assessment, and 59 were deaf, moved away, or were not Swedish speakers. Of the 4590 alive and eligible older adults, 1227 declined to participate, leaving a study population of 3363 (73.3%).



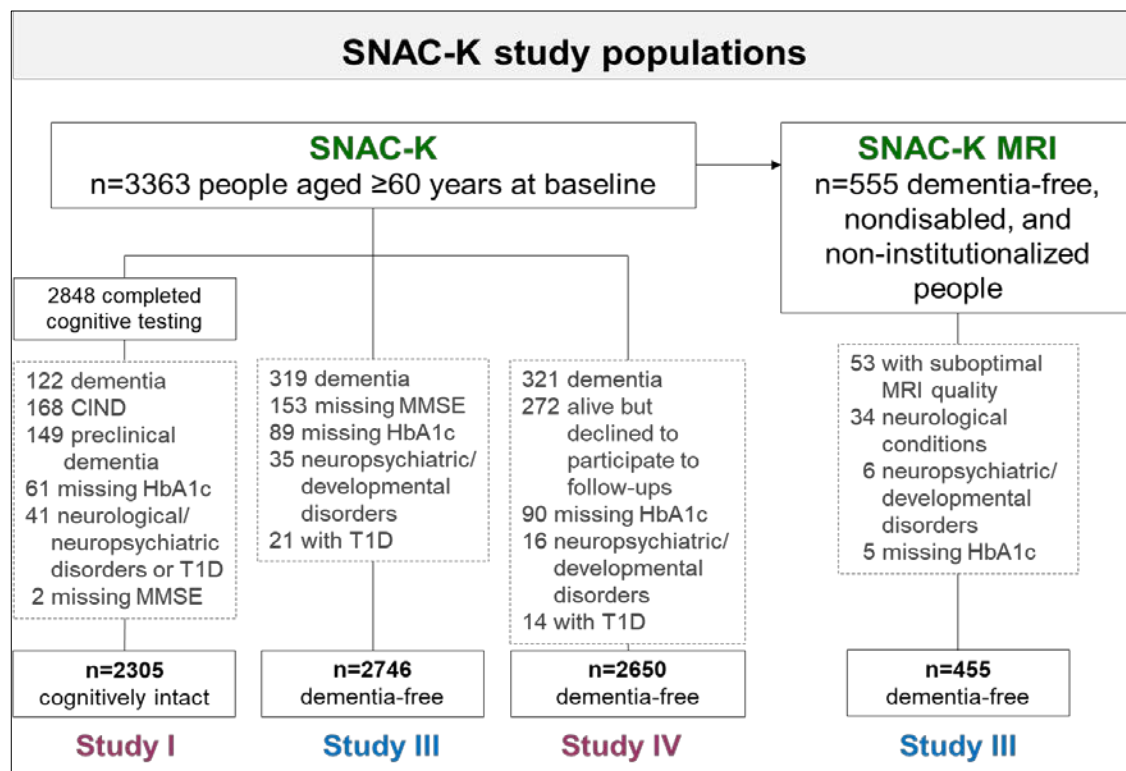
**Figure 4. The Swedish National Study on Aging and Care-Kungsholmen (SNAC-K) study design**  
The figure shows the SNAC-K assessment waves included in this thesis, from baseline (B) to the most recent follow-up for which data were available (F1=first follow-up, F2=second follow-up, F3=third follow-up).

**Study populations.** A schematic representation of the baseline populations and participants derived from SNAC-K and used in studies I, III, and IV is illustrated in **Figure 5**. In summary, Study I was cross-sectional and included 2305 cognitively intact participants who performed the cognitive test battery. Studies III (n=2746) and IV (n=2650), both longitudinal, followed dementia-free participants up to February 2013.

**Data collection.** At each wave, following standard protocols (available at <http://www.snac-k.se/>), physicians conducted clinical examinations and trained psychologists administered a comprehensive neuropsychological battery. Nurses collected data on sociodemographics, lifestyle factors, and medical history and measured anthropometrics and arterial parameters. Peripheral blood samples were taken from all participants.

### 3.1.2 The Swedish National Study on Aging and Care-Kungsholmen MRI study

During baseline (September 2001–October 2003), a subsample of 555 SNAC-K participants who did not live in an institution, were not disabled, and did not have dementia was randomly selected and invited to undergo a MRI examination. A total of 455 participants from the SNAC-K MRI study who did not have neurological or neuropsychiatric conditions were included in Study III (**Figure 5**).



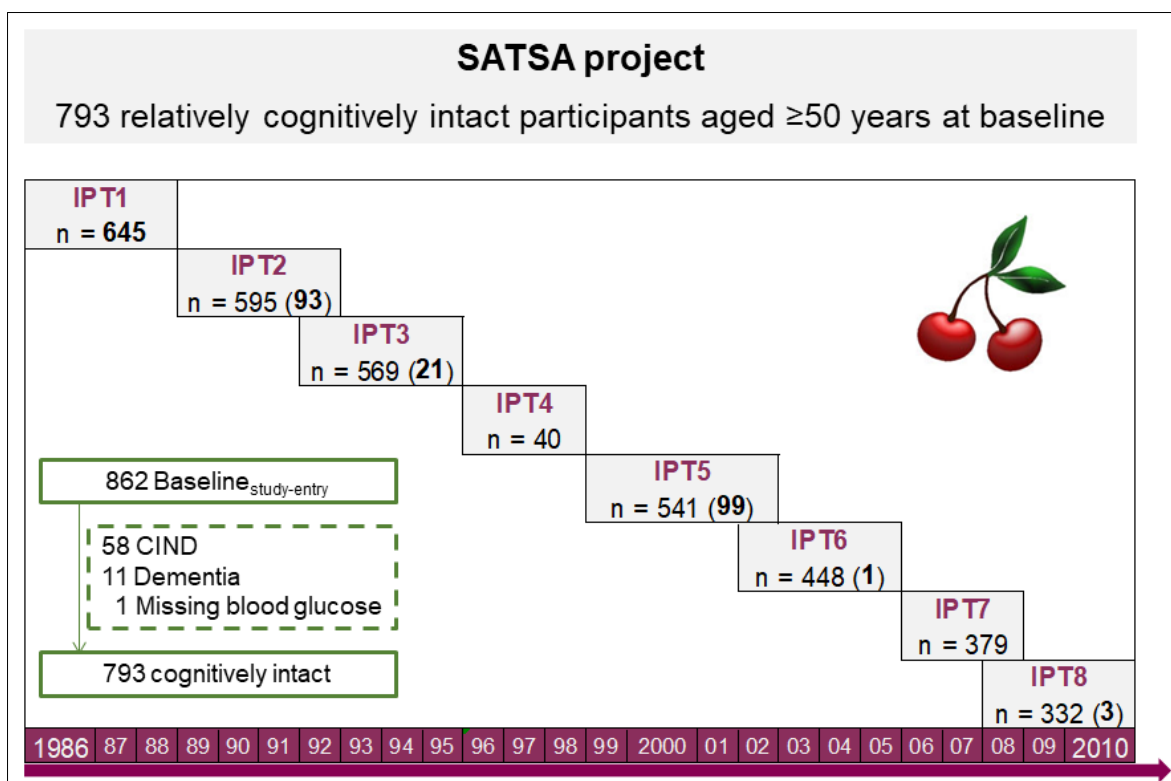
**Figure 5. SNAC-K and SNAC-K MRI study populations in studies I, III, and IV.**

Abbreviations: CIND, cognitive impairment-no dementia; HbA1c, glycated hemoglobin; MRI, magnetic resonance imaging; SNAC-K, Swedish National Study on Aging and Care-Kungsholmen; T1D, type 1 diabetes.

### 3.1.3 The Swedish Adoption/Twin Study of Aging study

SATSA is a population-based longitudinal study consisting of a subset of twin pairs from the Swedish Twin Registry (94). The twins from the registry who were reared apart and a matched sample of those who were reared together were interviewed by mailed questionnaire in 1984. Of the twins who responded to the first questionnaire, those who were aged >50 or older were further invited to undergo clinical examinations and cognitive assessments starting in 1986 (first in-person testing, n=645). Between 1986 and 2010, participants were assessed approximately every third year by trained nurses. Throughout the study follow-up period, eight waves of examinations were carried out. Additionally, during the study period, when twins in SATSA turned 50 years old, they were invited to participate in the follow-up examination that was ongoing. Because of the open-cohort design, the date of each participant's entry into the study was considered that person's baseline date. A total of 862 people participated in the baseline assessment and completed the cognitive protocol (**Figure 6**).

**Study population.** In Study II, participants with cognitive impairment-no dementia (CIND), dementia, and missing blood glucose concentration values were excluded, leaving a study population of 793 relatively cognitively intact participants at baseline (**Figure 6**).



**Figure 6. SATSA study design and population for Study II.**

The number in parentheses indicates those whose baseline was at each occasion after IPT1. The figure shows the waves of assessment in SATSA. The date at the participants' study entry was considered as baseline (n=862 including n=645 at IPT1, n=93 at IPT2, n=21 at IPT3, n=99 at IPT5, n=1 at IPT6, and n=3 at IPT8).

Abbreviations: CIND, cognitive impairment-no dementia; IPT, in-person testing; SATSA, Swedish Adoption/Twin Study of Aging.

**Data collection.** At each wave, information on demographics, lifestyle factors, medical conditions, current medications, and fasting status was collected through structured interview. Anthropometrics and arterial blood pressure were measured, and peripheral blood samples were taken from all participants.

### 3.2 ASSESSMENT OF DIABETES STATUS

In all datasets, diabetes status (diabetes, prediabetes, and glycemic control) was ascertained at baseline and follow-ups.

In SNAC-K, until December 2010, glycated hemoglobin (HbA1c [%]) was measured using Swedish Mono-S High Performance Liquid Chromatography. In accordance with the National Glycohemoglobin Standardization Program (NGSP), 1.1% was added to the HbA1c value to make them equivalent to international values (95). Beginning in January 2011, HbA1c was standardized using the International Federation of Clinical Chemistry (IFCC)'s method (96). A standard equation ( $\text{NGSP} = [0.09148 * \text{IFCC}] + 2.152$ ) (<http://www.ngsp.org/ifccngsp.asp>) was applied to convert from IFCC HbA1c (mmol/mol) to NGSP (%) (97).

**Diabetes and prediabetes.** Diabetes was identified based on self-reported medical history, glucose-lowering medications, medical records from the Swedish National Patient Register (ICD-10 code E11), or  $\text{HbA1c} \geq 6.5\%$  (98). Prediabetes was defined as HbA1c of 5.7%–6.4% in diabetes-free participants (98). In Study III, HbA1c was divided into quintiles (Q1 to Q5), ranging from normoglycemia to hyperglycemia (Q4 to Q5 [ $\text{HbA1c} \geq 5.8\%$ ]).

In SATSA, information on fasting status and fasting hours was collected by nurses. If the participant had fasted for  $\geq 8$  hours, the measurement taken was considered to be FBG. Diabetes was ascertained based on self-reported medical history, glucose-lowering medications, or  $\text{FBG} \geq 7.0$  mmol/L (or non-fasting blood glucose  $\geq 11$  mmol/L). Prediabetes was defined as FBG 5.6–7.0 mmol/L (or non-fasting blood glucose 7.8–11.0 mmol/L) in diabetes-free participants.

### 3.3 ASSESSMENT OF OUTCOMES

#### 3.3.1 Cognitive domains

In all datasets, global cognitive function was measured with the MMSE.

In SNAC-K, a battery of 10 cognitive tests (**Table 1**) was administered in a fixed order to assess the domains of perceptual speed, category fluency, letter fluency, semantic memory, and episodic memory. Cognitive domains were latent factors generated using structural equation modeling (99). In addition, the digit span forward and backward tests were



administered and participants' original score on these tests were used to assess attention/primary memory and working memory, respectively.

In SATSA, the cognitive battery included 11 cognitive tests (**Table 1**) that assessed four specific domains: verbal abilities, spatial/fluid abilities, memory, and processing speed. These domains were identified by principal component analysis (100).

**Table 1.** Cognitive assessment in SNAC-K and SATSA.

Cognitive assessment	SNAC-K	SATSA
Cognitive domains	Perceptual speed: Digit cancellation Patterns comparison Category fluency: Animals Professions Letter fluency: Letter A Letter F Semantic memory: 30-Multi-choice synonym test General knowledge Episodic memory: Word recall task Recognition task Attention/primary memory: Digit span forward Working memory: Digit span backwards	Perceptual speed: Digit symbol Figure identification Memory Digit span forward Digit span backward Thurstone's picture test Verbal abilities: Information test Synonyms (from WAIS) Analogies (from WAIS) Spatial/fluid abilities: Figure logic Kohs Block design Card rotation task

Abbreviations: SATSA, Swedish Adoption/Twin Study of Aging; SNAC-K, Swedish National Study on Aging and Care- Kungsholmen; WAIS, Wechsler Adult Intelligence Scale.

### 3.3.2 Cognitive impairment and dementia

In SNAC-K and SATSA, CIND was defined as the presence of objective cognitive impairment in any domain in absence of dementia (101). Age- and education-specific cognitive norms were calculated in the dementia-free study participants. At baseline, participants were identified as having CIND if they were 50–75 years and scored  $\geq 1$  standard deviation (SD) below the age- and education-specific mean MMSE score or were  $\geq 75$  years and scored  $\geq 2$  SDs below the age- and education-specific mean (102, 103). In both studies, dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (3rd or 4th edition) revised criteria.

In SNAC-K, all-cause dementia (hereafter, dementia) was diagnosed using a 3-step procedure. First, two examining physicians independently made preliminary diagnoses of dementia on the basis of the participant's physical, neurological, and cognitive status (steps

one and two). In case of discrepancy between the two diagnoses, in step three, a senior neurologist was consulted to reach a concordant diagnosis. For participants who died during follow-up, one physician extracted the diagnosis of dementia and dementia subtypes by consulting the available death certificate or medical records at hospital discharge when available. Differential diagnoses of Alzheimer's diseases (AD) was made in accordance with standard criteria in *The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association*, and differential diagnosis of vascular dementia (VaD) with the standard criteria in the *Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (104, 105). Mixed dementia was identified when participant had both features of AD and VaD.

In SATSA, dementia was diagnosed during a consensus conference based on all available information from the nurse visit, medical records, and cognitive assessment (106).

### 3.3.3 Brain MRI markers

**SNAC-K MRI Protocol.** Participants were scanned with a 1.5T MRI scanner (Philips Intera, The Netherlands). The protocol included an axial 3D T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle [FA] 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution  $0.94 \times 0.94$  mm, no gap, matrix  $256 \times 256$ ), and an axial turbo fluid-attenuated inversion recovery sequence (FLAIR; TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution  $0.90 \times 0.90$  mm, gap 1 mm, matrix  $256 \times 256$ ).

**Brain markers.** The volumes of grey matter (GMV), white matter (WMV), and cerebrospinal fluid were derived after segmentation of the T1-weighted images in SPM12 (Statistical Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm/>, Wellcome Trust Centre for Neuroimaging, FIL, London, UK), implemented in Matlab 10 (The Mathworks Inc., MA, USA), using the improved unified segmentation algorithm that employs an extended set of tissue-probability maps (107). The “light cleanup” option was used to further remove odd voxels from the images. Total brain tissue volume (TBTv) was obtained by summing GMV and WMV. Hippocampal volume (HV) was computed with automated segmentation of the T1-weighted images performed with the Freesurfer 5.1 image-analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) (108, 109). White matter hyperintensities volume (WMHV) was manually drawn on FLAIR images by a neuroimaging expert and further interpolated on the corresponding T1 images to compensate for the gap between slices in FLAIR (the intra-rater reliability was high [ICC >0.987]) (110). Total intracranial volume (TIV) was calculated by adding the GMV, WMV, and cerebrospinal fluid volumes. All segmentations were inspected by the SNAC-K neuroimaging expert. All MRI volumetric measurements were normalized by TIV and age (111, 112).

### 3.4 COVARIATES

#### 3.4.1 Sociodemographic factors

In all datasets, information on age, sex, and education were collected during the baseline assessment. Education was categorized as the highest level of formal education attained.

#### 3.4.2 Vascular risk factors

VRFs were measured at baseline. Smoking status was classified as never, former, or current. Alcohol consumption was categorized into never, occasional, or current ("current" included light to heavy drinking) (113). The physical activity variable was based on the intensity and frequency of physical exercise and divided into inactive, moderate, or heavy/vigorous (114, 115). Body weight and height were measured without shoes and without heavy clothes. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters ( $\text{kg/m}^2$ ) and categorized as underweight ( $<20.0$ ), normal weight (20–25), overweight ( $>25$ –30), and obese ( $\geq 30$ ).

#### 3.4.3 Vascular medical conditions and the *APOE* gene

Information on medical conditions was available through the Swedish National Patient Register, which covers all inpatient care since 1987 and outpatient care since 2001.

International Classification of Disease-tenth revision (ICD-10) criteria were used to define vascular medical conditions. During the physician's interview in SNAC-K and the nurse's interview in SATSA, arterial blood pressure was measured twice at a 5-min interval on the left arm in a sitting position. Diagnoses of vascular conditions were based on the physician's examination, self-report, medication use, or information from the Swedish National Patient Register and included hypertension (defined as blood pressure  $\geq 140/90$  mmHg), heart diseases (atrial fibrillation, bradycardias and conduction diseases, ischemic heart disease, cardiac valve disease, and heart failure), or cerebrovascular diseases (stroke or transient ischemic attack) (116, 117). The *APOE* gene was dichotomized into any  $\epsilon 4$  allele vs. no- $\epsilon 4$ .

#### 3.4.4 Mortality data

Participants' vital status was assessed using death certificates from the Swedish Cause of Death Registry and medical records at hospital discharge during the study period.

#### 3.4.5 Lifestyle

**Leisure activities.** At baseline, participants were asked how often in the past 12 months they had engaged in activities on a predefined list of 26 mental, social, or physical activities (118). Mental activities included those that primarily required mental engagement (i.e., reading books, playing chess/cards, playing a musical instrument, listening to music, using the Internet or playing computer games, and painting/drawing/working with clay). Level of engagement in mental activities was coded as low ( $\leq 1$  activity), moderate (2–3 activities), or high ( $\geq 4$  activities). Social activities included those that predominantly involved social

interactions (i.e., sports events, cinema/theatre/concerts, museums/art exhibitions, restaurants/bar/cafés, bingo, dancing, church service, traveling, volunteering, study circles/courses, and other social meetings). Level of engagement in social activities was coded as low (no activities), moderate (1 activity), or high ( $\geq 2$  activities). Physical activities were those for which the predominant component was light to vigorous physical activity (i.e., walking, jogging, bicycle riding, gym/golf/other sports, gardening work, strolling through the woods and countryside picking mushrooms/berries, going hunting/fishing, and home repair or car/machine/equipment repair). Level of engagement in physical activities was coded as low (performed less than once a week), moderate (performed at least once a week), or high (performed more than once a week). A *leisure activities index* was created by summing the level of engagement in mental, social, and physical activities (range 0–6), and coded as low (score 0–1), moderate (score 2–3), or high (score 4–6) engagement (118, 119).

**Social network.** At baseline, social network was assessed with a validated 10-item questionnaire that explored two aspects of social network: social connections and social support (120, 121). Raw scores on the items on social connections (marital status, cohabitation status, parenthood, friendships, and social network size; frequency of direct or remote contacts with parents, children, relatives, neighbors, and friends) and from the five items on social support (reported satisfaction with aforementioned contacts; perceived material and psychological support; sense of affinity with association members, relatives, and residence area; and being part of a group of friends) were standardized into z-scores and averaged to create an overall social connection index and a social support index. Each index was divided into tertiles on the basis of the score distribution: T1 (poor social network [ $\leq -0.27$ ] or support [ $\leq -0.10$ ]), T2 (moderate social network [ $-0.26$  to  $0.39$ ] or support [ $-0.09$  to  $0.33$ ]), and T3 (rich social network [ $>0.39$ ] or support [ $>0.33$ ]). Finally, an overall *social network index* was generated by averaging the social connection and social support indices. Social network was then divided into tertiles and coded as poor ( $\leq -0.14$ ), moderate ( $-0.13$  to  $0.30$ ), or rich ( $>0.30$ ), according to the tertile distribution.

### 3.5 STATISTICAL ANALYSIS

In all studies, baseline characteristics of participants by diabetes status (diabetes-free participants vs. those with prediabetes and diabetes) were compared using chi-square ( $\chi^2$ ) tests for categorical variables and one-way ANOVAs for continuous variables (tested with Bartlett's test of homogeneity of variance), followed by pairwise means comparisons with Bonferroni correction or quantile regression for heteroscedastic continuous variables. In studies I and II, cognitive domains were analyzed as separate outcome variables. The study-specific statistical methods are described below. An overview of the studies and methods included in this thesis is provided in **Table 2**.

**Study I.** Linear regressions were used to estimate the cross-sectional mean differences ( $\beta$ -coefficients and 95% confidence intervals [CIs]) in cognitive performance in diabetes-free

participants (reference) and those with prediabetes or diabetes. Interactions between diabetes and VRFs, vascular conditions, or *APOE*  $\epsilon$ 4 in predicting cognitive performance were tested.

**Study II.** Linear mixed-effects models—including unstructured variance-covariance matrix and random effects for intercept and slope for time—were used to explore the differences in annual rate of change in cognitive performance in diabetes-free participants (reference group) vs. those with prediabetes or diabetes, as function of age (time scale). Models included diabetes status (diabetes-free, prediabetes, diabetes), linear term for age at time of assessment, and their interaction terms (diabetes status  $\times$  linear age). The random effects (intercept and slope) accounted for both 1) the repeated measured for each person, and 2) the presence of twin pairs. The cognitive data were censored after dementia diagnosis.

**Study III.** Linear regression models were used to assess the cross-sectional associations between diabetes status and brain volumes at baseline. The longitudinal associations between diabetes status and annual rate of changes in global cognitive function or in the brain MRI markers were assessed with multivariable linear mixed-effect models—including unstructured variance-covariance matrix and random effects for intercept and slope for follow-up time (time scale). Models included diabetes status, linear term for annual follow-up time, and their interaction terms (diabetes status  $\times$  linear time). The relationship between hyperglycemia and cognitive decline was also tested with multivariable mixed-effect models.

**Study IV.** Incidence rates (IRs) per 1000 person-years of dementia and dementia subtypes were calculated as the number of new cases during follow-up divided by the person-years at risk. Cox regression models were used to estimate the hazard ratios (HRs) and 95% CIs of the association between diabetes status and dementia (all-cause and dementia subtypes). The time-scale was follow-up time, which was the time elapsed from baseline to dementia diagnoses or to death or the last examination. The proportional hazard assumption was verified by regressing Schoenfeld's residuals against follow-up time. No violation of proportionality was detected. The effect of having both diabetes and an active lifestyle (i.e., leisure activities or/and social network) on dementia risk was assessed by combining the levels of diabetes (yes, no) with the levels of active lifestyle.

All statistical models in the four studies (linear regressions, mixed-effect models, and Cox regressions) were multi-adjusted for baseline age, education, birth cohort, practice effect (Study II only), smoking, alcohol consumption, physical activity, BMI, CVDs, and/or *APOE*  $\epsilon$ 4.

In supplementary analyses, we first modeled diabetes status as a time-varying exposure (studies II and III). Second, we addressed potential reverse causality by censoring the outcomes at time of dementia diagnosis or excluding incident dementia during the follow-up period (studies III and IV). Finally, we performed multiple imputation by chained equation for missing values due to dropout (studies I to IV).

All tests were two-tailed, and  $p$ -values  $<0.05$  were considered statistically significant. Statistical analyses for all studies were performed with Stata SE 13.0 or 14.0 (StataCorp LP., College Station, Texas, USA).

**Table 2.** Overview of the four studies and methods included in this thesis.

Study	Title	Data sources and design	Prediabetes & diabetes assessment	Outcomes	Statistical analysis
<b>Study I</b>	Early cognitive deficits in type 2 diabetes	SNAC-K Cross-sectional	Diabetes: self-report, medication use, medical records, or HbA1c $\geq 6.5\%$ Prediabetes: HbA1c 5.7%–6.4% in diabetes-free participants	Cognitive performance at baseline	Linear regressions
<b>Study II</b>	Cognitive trajectories in prediabetes and diabetes	SATSA Longitudinal	Diabetes: self-report, medication use, or FBG $\geq 7.0$ mmol/L (RBG $\geq 11.0$ mmol/L). Prediabetes: FBG 5.6–7.0 mmol/L (or RBG 7.8–11.0 mmol/L)	Cognitive decline in 4 different domains over 23 years follow-up	Mixed-effect models with random intercept and slope, using age (years) as the time scale
<b>Study III</b>	Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions	SNAC-K and SNAC-K MRI Longitudinal	Diabetes: self-report, medication use, medical records, or HbA1c $\geq 6.5\%$ Prediabetes: HbA1c 5.7%–6.4% in diabetes-free participants	MMSE decline and brain MRI changes over 9 years follow-up	Mixed-effect models with random intercept and slope, using follow-up time (years) as the time scale
<b>Study IV</b>	An active lifestyle and a rich social network counteract the risk of dementia related to diabetes	SNAC-K Longitudinal	Diabetes: self-report, medication use, medical records, or HbA1c $\geq 6.5\%$ . Prediabetes: HbA1c 5.7%–6.4% in diabetes-free participants	Dementia over 10 years follow-up	Cox regression, using follow-up time (years) as the time scale

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; RBG, random blood glucose; SATSA, the Swedish Adoption/Twin Study of Aging; SNAC-K, Swedish National Study Aging and Care-Kungsholmen.

### 3.6 Ethical considerations

SNAC-K and SATSA received ethical permissions (registration numbers are reported in **Table 3**) from the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm. Informed consent (written or oral) were collected from all participants prior to their inclusion in the study, in accordance with the ethical principles for medical research involving humans stated in the World Medical Association's Declaration of Helsinki.

**Table 3.** List of ethical permits for SNAC-K and SATSA at baseline and follow-ups.

<b>DATASET</b>	<b>Registration numbers</b>
<b>SNAC-K</b>	
Wave I – baseline	01-114
Wave II – 1 <sup>st</sup> follow-up 78+	04-929/3
Wave III – 1 <sup>st</sup> follow-up 60-72, 2 <sup>nd</sup> follow-up 78+	Ö 26-2007
Wave IV – 2 <sup>nd</sup> follow-up 72, 3 <sup>rd</sup> follow-up 78+	2010/447-31/2
<b>SATSA</b>	84:61; 98-319; 2010/657-31/3
<b>Registries</b>	
SNAC-K permit to use register data	2009/595-32

Abbreviations: SNAC-K, Swedish National Study on Aging and Care-Kungsholmen; SATSA, the Swedish Adoption/Twin Study of Aging

In SNAC-K, participants were informed both by letter and in person. Two weeks before assessment, a letter was sent to explain the study's purpose and duration, interview process, and the importance of participation. Participants were informed that participation was voluntary and that they could withdraw at any time and without explanation. If a person had cognitive impairment, a proxy (i.e., close family member or guardian) was asked for consent. Afterward, nurses telephoned only those who agreed to participate and scheduled an appointment. The examination process took place in a friendly and comfortable environment. During the examination, if the participant expressed anxiousness or discomfort, the interview was terminated. As part of the informed consent process, participants were assured that their data would remain confidential and anonymous.

Similarly, in SATSA, all participants received a letter that described the purpose, content, and duration of the study and were assured confidentiality and anonymity as part of the informed consent process. Participants were informed that their involvement in the study was voluntary and that they were free to drop out at any point in time.

For data collected through the registry system, ethical requirements clearly state that the consent must be voluntary. This means that information on the health status of participants who dropped out was not available from registries, with the exception of data on vital status (if participants was alive or died), which is not covered by privacy law. Risks to privacy have been further minimized by assigning one administrator to access the registries and limiting the information accessible. In all datasets, researchers obtained anonymized data without any reference to a person's name or personal identification number; data were tagged with only a study-specific ID number.



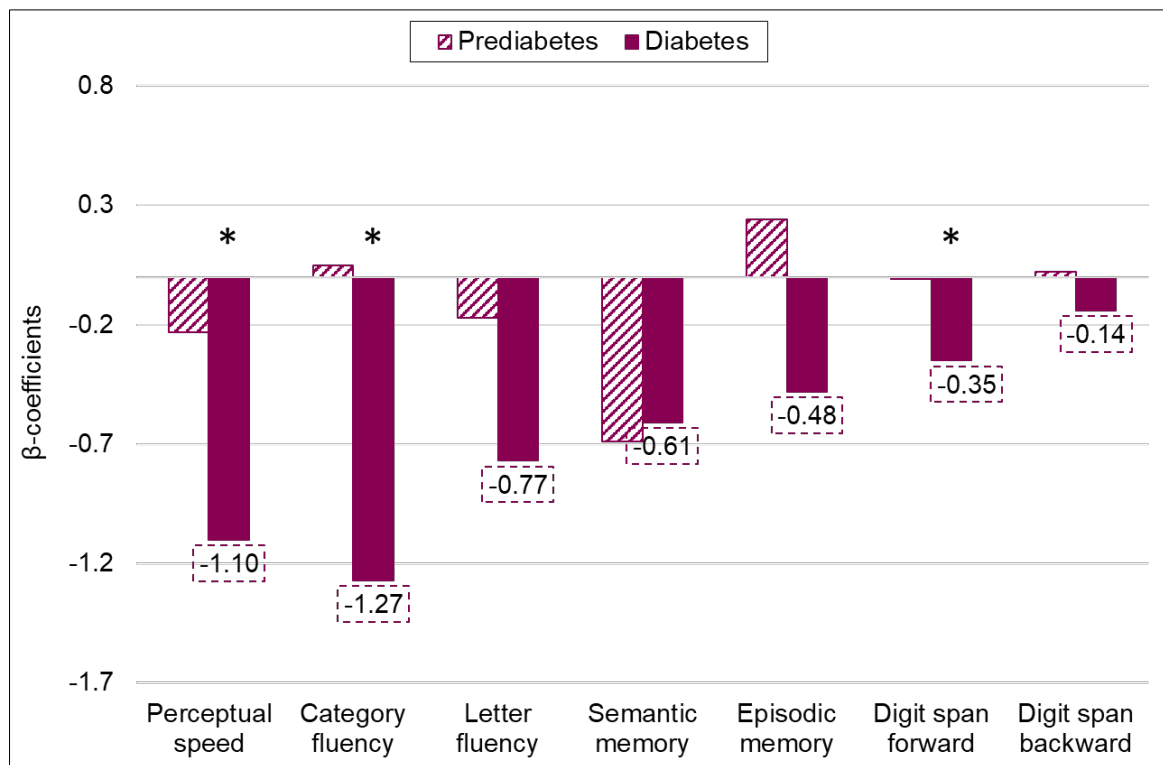
## 4 RESULTS

This section reports the main results of the thesis. For more details on the results of each study, please refer to the published papers and the manuscripts included in the thesis.

### 4.1 DIABETES AND COGNITIVE DOMAIN-SPECIFIC DEFICITS

In Study I, of the 2305 cognitively intact participants, 571 (24.8%) had prediabetes. One hundred ninety-six (8.5%) had diabetes, 144 of whom had uncontrolled diabetes. Participants with prediabetes or diabetes were more likely than those without diabetes to be older, male, and more physically active; consume less alcohol; and to have fewer years of formal education, higher BMI, hypertension, heart disease, and/or lower MMSE scores. Participants with prediabetes or diabetes had lower mean performance in all cognitive domains than diabetes-free older adults.

**Early deficits in cognitive domains associated with diabetes.** Age, sex, and education-adjusted linear regressions showed that participants with diabetes had lower perceptual speed ( $\beta$  -1.98 [95% CI -1.98, -0.23];  $p=0.014$ ), category fluency ( $\beta$  -1.27 [95% CI -2.52, -0.03];  $p=0.045$ ), and digit span forward ( $\beta$  -0.35 [95% CI -0.54, -0.17];  $p=0.000$ ) performance than those who were diabetes-free (**Figure 7**). No significant association between prediabetes and cognitive performance was detected. After multi-adjustment for VRFs, physical activity, CVDs, and depression, only the association between diabetes and poor performance in the digit span forward test remained significant ( $\beta$  -0.21 [95% CI -0.39, -0.02];  $p=0.027$ ).



**Figure 7. Association between prediabetes and diabetes and performance across cognitive domains.**

Mean differences ( $\beta$ -coefficients) in cognitive performance in participants with prediabetes (striped bar) or diabetes (solid purple bar). The reference group consisted of those who were diabetes-free, and the results were adjusted for age, sex, and education.

\*  $p$ -values for the comparisons between people with prediabetes or diabetes and those who were diabetes-free were  $<0.05$ .

**Factors modulating the link between diabetes and cognitive deficits.** We investigated whether having diabetes and VRFs, diabetes and CVDs, or diabetes and *APOE*  $\epsilon 4$  predicted cognitive performance in the different domains. Significant and marginally significant two-way interactions ( $p$ -values ranging from 0.020 to 0.062) suggested differential cognitive performance in people with and people without smoking history, those who were and were not overweight/obese, and those who did or did not have CVDs. Diabetes combined with current/former smoking, overweight/obesity, or CVDs was associated with poorer cognitive perceptual speed (smoking:  $\beta$  -1.59 [95% CI -2.50, -0.35]; overweight/obesity:  $\beta$  -1.63 [95% CI -2.58, -0.67]; CVDs:  $\beta$  -2.90 [95% CI -4.01, -1.80]) and category fluency performance (smoking:  $\beta$  -1.69 [95% CI -3.21, -0.18]; overweight/obesity:  $\beta$  -1.36 [95% CI -2.75, -0.04]; CVDs:  $\beta$  -2.44 [95% CI -4.05, -0.83]), than being diabetes-free and not having the respective risk factors (**Figure 8**, panels A–C). In stratified analyses by *APOE*  $\epsilon 4$  allele, people who had diabetes and did not carry the  $\epsilon 4$  allele performed worse in perceptual speed ( $\beta$  -1.11 [95% CI -2.15, -0.06]) and digit span forward ( $\beta$  -0.36 [95% CI -0.58, -0.14]) tasks than people who were diabetes-free and did not carry the  $\epsilon 4$  allele (**Figure 8**, panel D). However, the differences in digit span forward performance were not present in people who carried the  $\epsilon 4$  allele.

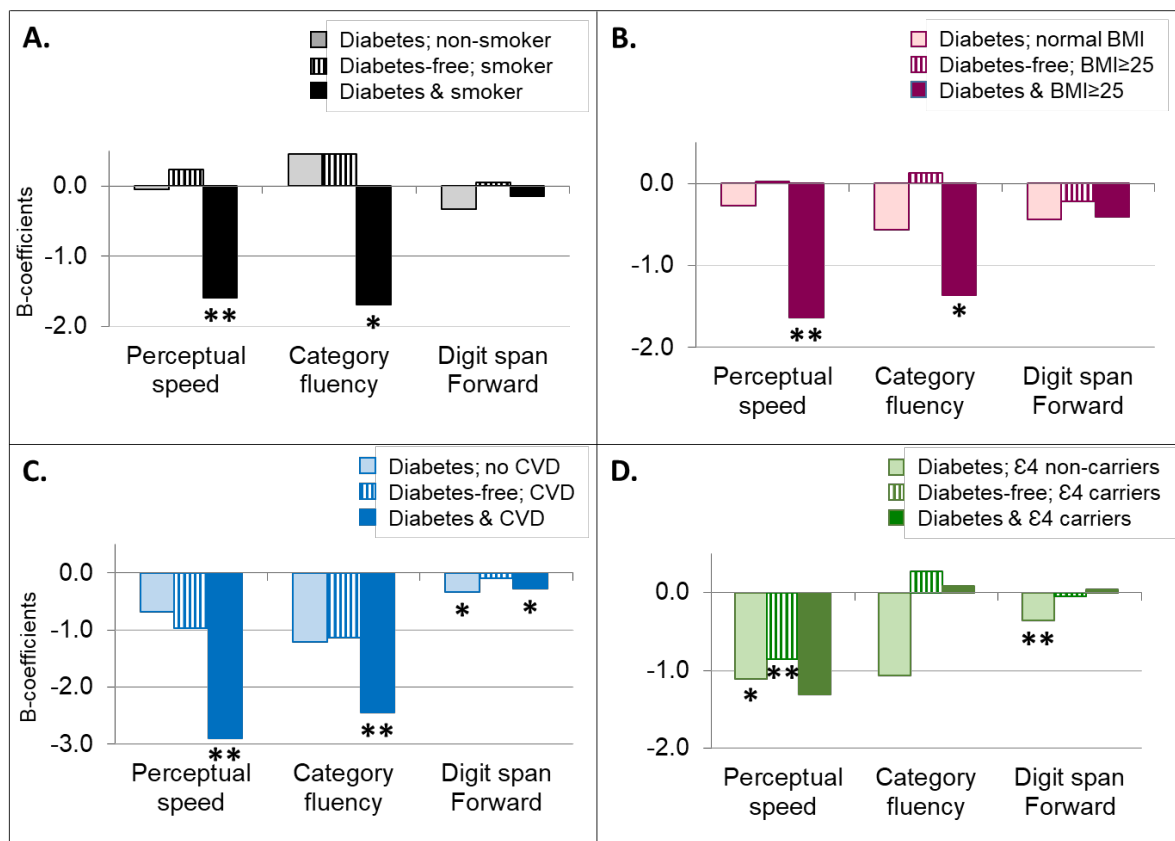


Figure 8. Association between combinations of risk factors (diabetes and vascular risk factors, diabetes and cardio- and cerebrovascular disorders, and diabetes and the apolipoprotein E gene-ε4 allele) and cognitive function. The figure shows the multi-adjusted (by age, sex, education, and all remaining covariates)  $\beta$ -coefficients estimated from four separate linear regression models for the associations between A) diabetes and smoking (reference group: people who were diabetes-free and did not smoke), B) diabetes and BMI (reference group: people who were diabetes-free and had a normal BMI), C) diabetes and CVD (reference group: people who were diabetes-free and did not have CVD), and D) diabetes and *APOE* ε4 (reference group: people who were diabetes-free and did not carry the ε4 allele) and cognitive performance in three domains.

\*  $p$ -value < 0.05; \*\*  $p$ -value < 0.01.

Abbreviations: *APOE* ε4, apolipoprotein E gene-ε4 allele; BMI, body mass index; CVDs, cardio- and cerebrovascular disorders.

## 4.2 TRAJECTORIES OF COGNITIVE DECLINE IN PEOPLE WITH PREDIABETES OR DIABETES

In Study II, of the 793 cognitively intact older adults at baseline in SATSA, 68 (8.6%) had prediabetes and 45 (5.7%) had diabetes. Participants with prediabetes or diabetes were older than those who were diabetes-free. They were also more likely to be overweight or obese, to have hypertension, to have a lower MMSE score, and to perform worse in tests of perceptual speed and memory. The three groups did not differ significantly with regard to other VRFs, CVD, or whether they carried the *APOE* ε4 allele. During follow-up (mean  $13.7 \pm 6.6$  years [range=3–23 years]), 361 (45.5%) participants died, 284 (35.8%) participated in all waves, 120 (15.1%) participated in at least two waves, and 28 (3.5%) only participated in the baseline assessment.

In Study III, of the 2746 dementia-free older participants at baseline in SNAC-K (947 [34.5%] had prediabetes and 242 [8.8%] had diabetes), 651 (23.7%) died over a mean follow-up of  $6.4 \pm 1.7$  years (range=2.1–10.3 years).

**Table 4** shows the differences between SATSA and SNAC-K in baseline characteristics of participants and those who died during follow-up. Overall, the differences between participants and those who died were similar in the two datasets. Those who died were, on average, older than those who participated. They were also more likely to have a low level of education, consume less alcohol, and have worse health status than participants.

**Table 4.** Baseline characteristics of participants and of those who died during follow-up in SATSA and SNAC-K.

Baseline characteristics	SATSA study			SNAC-K study		
	Participants*	Death	<i>p</i>	Participants	Death	<i>p</i>
	n=404	n=361		n=1642	n=651	
Age (years)	58.4 ± 6.7	69.0 ± 7.4	<0.001	68.8 ± 8.4	81.8 ± 8.9	<0.001
Female sex	250 (61.9)	200 (55.4)	0.07	1023 (62.3)	388 (59.6)	0.231
Low education †	187 (48.1)	112 (31.9)	<0.001	1481 (90.2)	500 (77.0)	<0.001
Currently smokers	181 (46.5)	162 (46.4)	0.976	908 (55.6)	348 (53.6)	0.382
Alcohol consumption	353 (87.4)	288 (79.8)	0.004	1252 (76.5)	338 (52.4)	<0.001
BMI (kg/m <sup>2</sup> )						
Underweight (<20)	16 (4.0)	20 (5.5)	0.487	46 (2.8)	74 (11.4)	<0.001
Normal (≥20–25)	184 (45.5)	149 (41.3)		682 (41.5)	306 (47.0)	
Overweight (≥25–30)	152 (37.6)	148 (41.0)		688 (41.9)	211 (32.4)	
Obese (≥30)	52 (37.6)	44 (12.2)		226 (13.8)	60 (9.2)	
Diabetes status						
Diabetes-free	359 (88.9)	299 (82.8)		1008 (61.4)	306 (47.0)	
Prediabetes	37 (9.2)	26 (7.2)	<0.001	523 (31.9)	254 (39.0)	<0.001
Diabetes	8 (2.0)	36 (10.0)		111 (6.8)	91 (14.0)	
Hypertension	168 (41.6)	200 (55.4)	<0.001	1116 (68.0)	474 (72.8)	0.023
Heart diseases	33 (8.4)	62 (17.3)	<0.001	230 (14.0)	298 (45.8)	<0.001
Cerebrovascular disease	1 (0.3)	6 (1.7)	0.043	59 (3.6)	73 (11.2)	<0.001
Any APOE ε4	103 (27.4)	88 (33.9)	0.094			
MMSE score	28.6 ± 1.3	28.9 ± 1.5	<0.001	29.2 ± 1.0	28.0 ± 1.8	<0.001

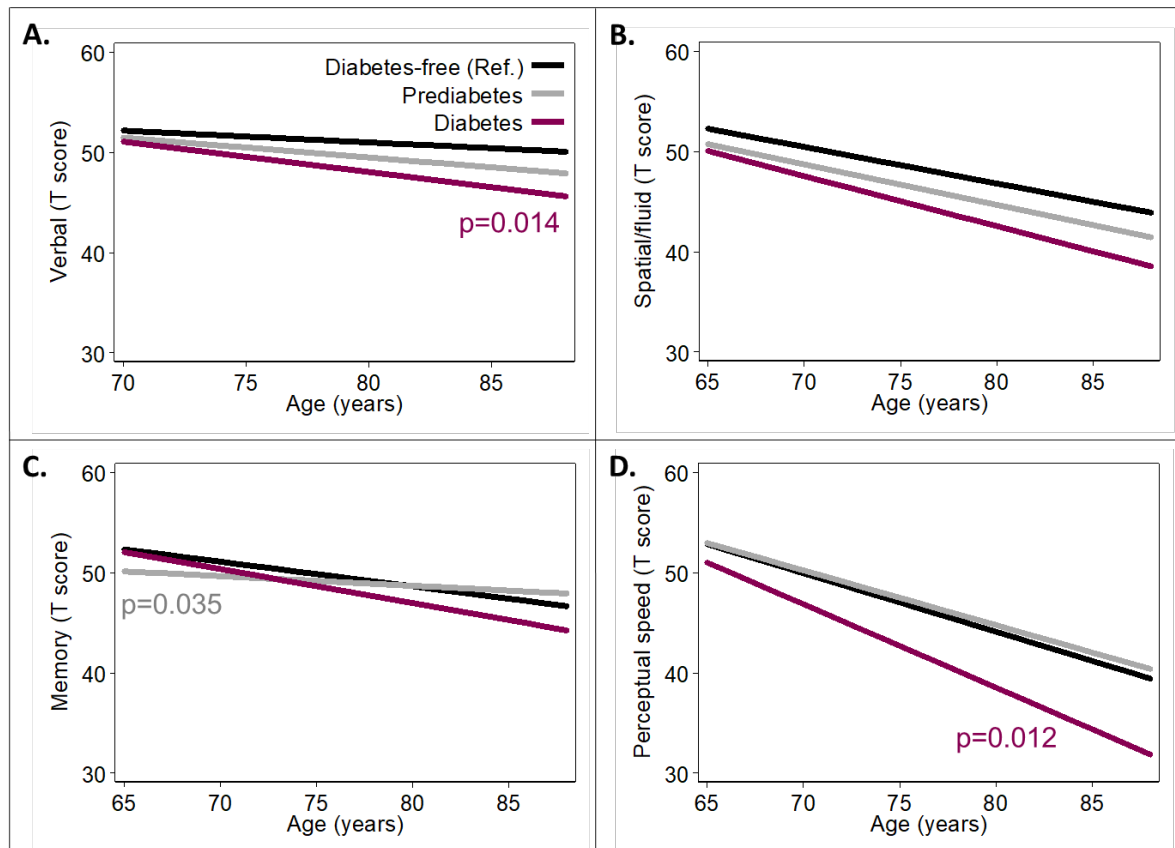
Data are presented as mean ± standard deviations or proportion (%).

\* Participated in at least two or all waves of assessment.

† A low level of education was defined as <9 years of schooling (SATSA) or an elementary school education (SNAC-K).

Abbreviations: APOE ε4, apolipoprotein E gene-ε4 allele; BMI, body mass index; MMSE, Mini-Mental State Examination; SATSA, The Swedish Adoption/Twin Study of Aging; SNAC-K, Swedish National Study on Aging and Care.

**Cognitive trajectories in people with prediabetes and diabetes.** In SATSA, people with diabetes had a faster decline in verbal abilities over time ( $\beta_{\text{slope}} -0.19$  [95% CI -0.33, -0.04];  $p=0.014$ ) and perceptual speed ( $\beta_{\text{slope}} -0.25$  [95% CI -0.44, -0.05];  $p=0.012$ ) than those who were diabetes-free. Participants with prediabetes had worse memory performance at age 65 ( $\beta_{\text{intercept}} -2.19$  [95% CI -4.16, -0.10];  $p=0.035$ ) than those who were diabetes-free, memory function in those with prediabetes declined less steeply over time ( $\beta_{\text{slope}} 0.15$  [95% CI 0.00, -0.30];  $p=0.050$ ) (Figure 9). Results were similar after adjustment for VRFs and CVDs.



**Figure 9. Trajectories of cognitive decline by diabetes status across domains (Study II).**

The figure shows the trajectories of cognitive decline, as a function of age, in verbal abilities (A), spatial/fluid abilities (B), memory (C), and perceptual speed (D) in older adults with prediabetes (grey line), with diabetes (purple line), and who were diabetes-free (black line [reference group]).  $\beta$ -coefficients for intercepts and slopes were estimated with mixed-effects models adjusted for sex, education, birth cohort, and practice effects.  $P$ -values in purple indicate significance levels of the additional decline in people with diabetes, and  $p$ -values in grey indicate the significance levels of the intercept in people with prediabetes.

We further examined the trajectories of global cognitive decline (MMSE score) over follow-up in SNAC-K. After adjustment for baseline age, sex, education, VRFs, and CVDs, prediabetes ( $\beta_{\text{slope}} -0.05$  [95% CI -0.09, -0.01];  $p=0.008$ ) and diabetes ( $\beta_{\text{slope}} -0.10$  [95% CI -0.17, -0.03];  $p=0.005$ ) were independently associated with a faster global decline over the follow-up than being diabetes-free. When MMSE data were censored after dementia

diagnosis, the association between prediabetes and faster decline remained similar to the associations observed in the initial analysis. However, global cognition declined less steeply (and statistically non-significantly) in people with diabetes than in those who were diabetes-free ( $\beta_{\text{slope}} -0.03$  [95% CI -0.08, 0.01];  $p=0.144$ ). As HbA1c was dose-dependently associated with faster cognitive decline, regardless diabetes status, we further examined the relationship between hyperglycemia (higher quintiles of HbA1c) and changes in MMSE score. The results showed that the higher quintiles of HbA1c ( $n=899$  [Q4-Q5: HbA1c  $\geq 5.8\%$ ]), which corresponded to hyperglycemia, were independently associated with faster cognitive decline (**Table 5**). The reference group in the analyses consisted of those with normoglycemia ( $n=686$  [Q1: HbA1c 4.3–5.4%]).

**Table 5.**  $\beta$ -coefficients (95% confidence intervals) of the association between annual changes in Mini-Mental State Examination scores and quintiles of glycated hemoglobin in SNAC-K. Quintile 1, in which HbA1c levels corresponded to normoglycemia, was the reference group. In quintiles 4 and 5, HbA1c levels corresponded to hyperglycemia.

HbA1c (quintiles) $\times$ time (years)	Basic adjusted $\beta$ (95% CI) *	$p$	Multi-adjusted $\beta$ (95% CI) †	$p$
Q1 (HbA1c 4.3–5.4%) $\times$ time	Reference		Reference	
Q2-Q3 (HbA1c $\geq 5.4$ –5.8%) $\times$ time	-0.03 (-0.06; -0.004)	0.023	-0.03 (-0.06; 0.01)	0.020
Q4-Q5 (HbA1c $\geq 5.8\%$ ) $\times$ time	-0.05 (-0.08; -0.02)	0.002	-0.05 (-0.08; -0.02)	0.003

MMSE data were censored after dementia diagnosis.

\* Adjusted for baseline age, sex, and education.

† Adjusted for baseline age, sex, education, smoking, alcohol consumption, physical activity, BMI, and CVDs.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardio- and cerebrovascular disorders; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination; Q, quintile; SNAC-K, Swedish National Study of Aging and Care-Kungsholmen.

### 4.3 PREDIABETES, DIABETES, AND STRUCTURAL BRAIN MARKERS

In Study III, in the SNAC-K MRI sample, 455 participants (136 [29.9%] had prediabetes and 32 [7.0%] had diabetes) were followed for an average of  $5.7 \pm 0.7$  years (range=2.9–7.1 years). Participants with prediabetes or diabetes were older and more likely to have heart disease than those who were diabetes-free. On average, they also had smaller TBTv, GMV, and WMV and higher WMHV than those who were diabetes-free. Thirty-nine participants (8.6%) died during follow-up.

**Prediabetes, diabetes, and brain MRI changes.** In multi-adjusted linear regression models, prediabetes was independently associated with smaller TBTv, especially WMV, and diabetes was associated with larger WMHV (**Table 6**). HV was not associated with prediabetes or diabetes. The reference group in the models consisted of those who were diabetes-free.

**Table 6.**  $\beta$ -coefficients (95% confidence intervals) of the cross-sectional associations between magnetic resonance imaging markers and diabetes status from linear regression models

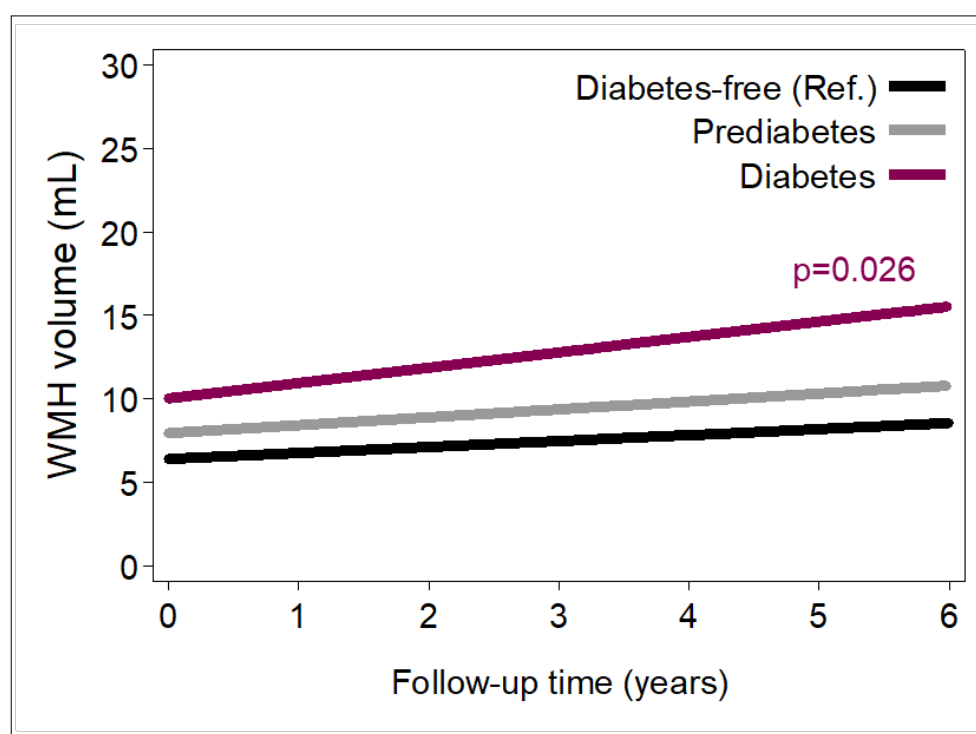
Brain volumes *	Prediabetes (n=136)		Diabetes (n=32)	
	$\beta$ (95% CI) †	<i>p</i>	$\beta$ (95% CI) †	<i>p</i>
Total brain tissue	-18.7 (-33.1; -4.3)	0.011	-18.3 (-44.3; 7.7)	0.167
Grey matter	-9.03 (-19.4; 1.28)	0.086	-5.80 (-24.4; 12.8)	0.540
Hippocampus	-0.08 (-0.24; 0.09)	0.354	-0.09 (-0.39; 0.21)	0.566
White matter	-9.67 (-18.7; -0.68)	0.035	-12.5 (-28.7; 3.67)	0.129
White matter hyperintensities	1.56 (-0.33; 3.46)	0.106	3.49 (0.06; 6.92)	0.046

\* Brain volumes (mL) were adjusted for intracranial volume and age.

† Adjusted for sex, education, BMI, hypertension, and heart diseases.

Abbreviations: BMI, body mass index; CI, confidence interval.

During follow-up, multi-adjusted mixed-effect models that compared those with prediabetes or diabetes with the reference group of participants who were diabetes-free showed that diabetes was independently associated with a faster increase in WMHV ( $\beta_{\text{slope}}$  0.56 [95% CI 0.07, 1.05];  $p=0.026$ ) (**Figure 10**). This finding suggests that cerebral microvascular lesions accumulate faster in people with diabetes than in those who are diabetes-free.



**Figure 10.** Trajectories of change in the volume of white matter hyperintensities over six years by diabetes status.

The figure shows white matter hyperintensity trajectories as a function of follow-up time in people with prediabetes (grey line), people with diabetes (purple line), and those who were diabetes-free (black line [reference group]). Volume of white matter hyperintensities (mL) was adjusted for intracranial volume and age.  $\beta$ -coefficients for intercepts and slopes were estimated with mixed-effects models adjusted for sex, education, BMI, hypertension, and heart disease.

Abbreviations: BMI, body mass index; WMH, white matter hyperintensity.

Multi-adjusted mixed models showed that regardless of a person's diabetes status, there was a dose-dependent association between hyperglycemia (Q4-Q5 [HbA1c  $\geq 5.8\%$ ]) and smaller TBTV ( $\beta_{\text{intercept}} -24.2$  [95% CI -41.5, -6.87];  $p=0.006$ ), particularly WMHV ( $\beta_{\text{intercept}} -12.6$  [95% CI -23.6, -1.60];  $p=0.025$ ), as well as greater WMHV ( $\beta_{\text{intercept}} 3.32$  [95% CI 1.04, 5.60];  $p=0.004$ ) and faster increase in WMHV over follow-up ( $\beta_{\text{slope}} 0.30$  [95% CI -0.09, 0.60];  $p=0.058$ ). The reference group consisted of participants with normoglycemia.

#### 4.4 PREDIABETES, DIABETES, AND RISK OF DEMENTIA

In Study IV, the 2696 participants in SNAC-K who were dementia-free at baseline, including 921 (34.8%) with prediabetes and 243 (9.2%) with diabetes, were followed for  $6.4 \pm 1.8$  years (range=2.1–10.3 years). During follow-up, 691 (26.1%) died and 229 (8.6%) declined to participate in follow-up or had moved. Those who died were older and more likely to have a lower level of education, lower BMI, more CVDs, diabetes, and lower MMSE score at baseline than the 1729 who were alive and participated in the SNAC-K follow-ups.

A total of 246 (9.1%) participants were diagnosed with dementia (IR=15.4 [95% CI 13.6–17.5] per 1000 person-years) over follow-up, including 128 (52.0%) with AD, 25 (10.2%) with VaD, and 33 (13.4%) with mixed dementia. At baseline, those with incident dementia were older, more likely to be female, and less likely to have a high level of education than older adults diagnosed with dementia during follow-up. They were also more likely to have lower BMI, heart disease, CVD, diabetes, a lower MMSE score, and at least one *APOE*  $\epsilon 4$  allele. Finally, they were more likely to be less engaged in mental, social, and physical leisure activities and to have a poor social network.

The incidence rates of dementia and its subtypes per 1000 person-years are displayed in **Table 7**. In multi-adjusted Cox regression models, diabetes was associated with an increased risk of dementia, in particular vascular dementia and, marginally, mixed dementia.



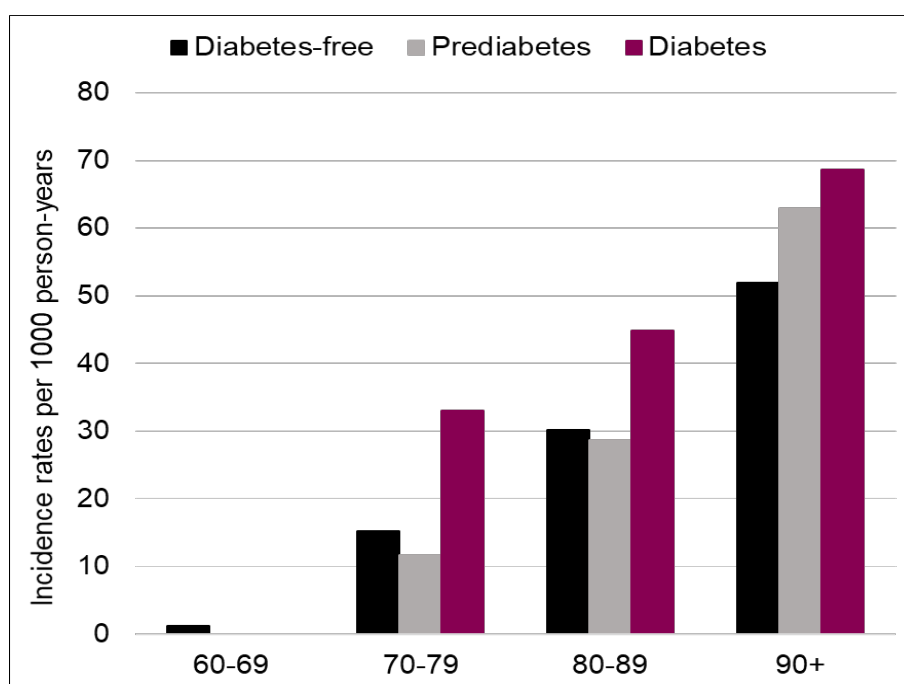
**Table 7.** Incidence rates of all-cause dementia, Alzheimer's disease, vascular dementia, and mixed dementia (per 1000 person-years) by diabetes status and hazard ratios and 95% confidence intervals of the association between dementia, prediabetes, and diabetes.

Dementia	No. events/ Person-year	IR (95% CI)	Cox regression models	
			HR (95% CI) *	p
All-cause				
Diabetes-free	121/9368	13.3 (11.2–15.9)	Reference	
Prediabetes	88/5517	16.0 (12.9–19.7)	0.97 (0.72–1.30)	0.835
Diabetes	37/1339	27.6 (20.0–38.1)	2.23 (1.49–3.33)	0.000
AD				
Diabetes-free	67/9068	7.39 (5.85–9.39)	Reference	
Prediabetes	49/5517	8.88 (6.71–11.8)	0.97 (0.66–1.43)	0.894
Diabetes	12/1339	8.96 (5.09–15.8)	1.34 (0.69–2.59)	0.388
VaD				
Diabetes-free	10/9068	1.10 (0.59–2.05)	Reference	
Prediabetes	7/5517	1.27 (0.60–2.66)	1.20 (0.44–3.33)	0.718
Diabetes	8/1339	5.97 (2.99–11.9)	7.11 (2.21–22.9)	0.001
Mixed				
Diabetes-free	12/9068	1.32 (0.75–2.33)	Reference	
Prediabetes	15/5517	2.72 (1.64–4.51)	1.39 (0.63–3.05)	0.410
Diabetes	6/1339	4.48 (2.01–9.97)	2.55 (0.90–7.23)	0.078

\* Adjusted for baseline age, sex, education, smoking, BMI, CVD, and *APOE*  $\epsilon$ 4.

Abbreviations: AD, Alzheimer's disease; *APOE*  $\epsilon$ 4, apolipoprotein E gene- $\epsilon$ 4 allele; BMI, body mass index; CI, confidence interval; CVD, cardio- and cerebrovascular disorders; HR, hazard ratio; IR, incident rate; Mixed, mixed dementia; VaD, vascular dementia.

**Figure 11** shows the age-specific incident rate of dementia by diabetes status. As expected, the overall incidence of dementia increased with age in people who were diabetes-free, those with prediabetes, and those with diabetes



**Figure 11.** Age-specific incidence rates of dementia per 1000 person-years by diabetes status.

## 4.5 THE EFFECT OF ACTIVE LIFESTYLE PLUS DIABETES ON DEMENTIA

Moderate (adjusted HR=0.59, 95% CI 0.42–0.82) or high (adjusted HR=0.44, 95% CI 0.26–0.74) engagement leisure activities and moderate (adjusted HR=0.73, 95% CI 0.53–1.01) or rich (adjusted HR=0.55, 95% CI 0.38–0.81) social network were associated with a decreased risk of dementia. We therefore merged them into single categories: “moderate-to-high” for leisure activities and “moderate-to-rich” for social network. To assess the potential that an active lifestyle would counteract diabetes-related dementia risk, we created an indicator variable. The variable combined diabetes status (no vs. yes) with level of leisure activity (low vs. moderate-to-high) or social network (low vs. moderate-to-rich). This dummy variable divided the participants in four groups: 1) those who were diabetes-free and had a low level of leisure activity and a poor social network (“diabetes-free inactive”); 2) those who were diabetes-free but at had at least one active leisure activity or a rich social network (“diabetes-free active”); 3) those with diabetes, a low level of leisure activity, and a poor social network (“diabetes inactive”); and 4) those with diabetes, at least one active leisure activity, or a rich social network (“diabetes active”).

Those in the “diabetes inactive” group had a nearly 6-fold higher risk of dementia than those in the “diabetes-free active” group. The adjusted HR of dementia for participants with diabetes and an active lifestyle was higher than in the “diabetes-free active” group but substantially lower than the risk in the “diabetes inactive” group (HR=1.94, 95% CI 1.09–3.50). Indeed, the “diabetes active” group’s risk was similar to that of diabetes-free older adults with an inactive lifestyle (HR=1.66, 95% CI 0.96–2.89;  $p=0.071$ ).

## 4.6 SUPPLEMENTARY ANALYSIS

**Time-varying diabetes status.** Prediabetes is not a chronic condition; people with prediabetes may transition to having diabetes or being diabetes-free. We therefore modeled diabetes status as a time-varying exposure in the mixed-effect models, accounting for the length of time that each participant was in each stage before the transition to another stage. In Study II, no association between time-varying prediabetes and domain-specific cognitive decline was observed. In Study III, the association between time-varying prediabetes and cognitive decline was statistically significant, but the association between time-varying prediabetes and volumetric brain changes was not.

**Possible reverse causation.** In all the longitudinal studies (II–IV), we addressed potential reverse causality by censoring the outcome(s) at the time of dementia diagnosis, excluding incident dementia during the full follow-up period or during the first follow-up, or excluding participants with baseline MMSE  $\leq 27$ . These results were very similar to those of the initial analyses.

**Multiple imputation.** In all, studies, we addressed potential bias related to missing values with multiple imputation. Results were not altered.

## 5 DISCUSSION

This thesis investigated the impact of prediabetes and diabetes on different stages of cognitive function during aging—from the early appearance of cognitive deficits, through cognitive decline, to dementia. It also explored the biological mechanisms underlying diabetes-related cognitive decline and identified factors that might protect people with diabetes from dementia.

### 5.1 INTERPRETATION OF THE MAIN FINDINGS

#### 5.1.1 Diabetes and cognitive aging: from cognitive deficits to dementia

The findings of this thesis support the notion that diabetes affects the whole process of cognitive aging, from being cognitively intact to dementia. The results of studies I and II showed that some cognitive domains appear to be more sensitive than others to the impact of diabetes. Indeed, diabetes was related to poor performance in perceptual speed, category fluency, and attention/primary memory in cognitively intact older people (122). Diabetes was also associated with fast decline in perceptual speed and verbal abilities in relatively cognitively intact older adults (117). However, the association between diabetes and episodic memory was not evident in either cross-sectional or longitudinal analyses (117, 122). These findings suggest that diabetes is associated with early deficits in the cognitive domains of processing speed, executive function, and attention/primary memory, and furthermore that these domains decline faster than others over time. Finally, our results showed that diabetes was associated with double the risk of dementia (especially of vascular origin), but that this risk could be counteracted, at least in part, by an active lifestyle and a rich social network. This suggests the presence of mechanisms that can compensate for and might protect against dementia in people with diabetes.

Although studies consistently observe an association between diabetes and cognitive deficits, the domains that are impaired by diabetes early in cognitive deterioration have remained unclear. The results of previous research on the associations between diabetes and cognitive function in the different subdomains of memory (episodic, semantic, and working) and between diabetes and processing speed, attention and executive function, visuospatial abilities, and verbal abilities have been highly heterogeneous (see Appendices 1 and 2) (123). This heterogeneity is linked to methodological limitations. This doctoral project was able to address some of these methodological concerns by using composite domain measures extracted by structural equation modeling or principal-component analysis and diagnostic tests for prediabetes and diabetes (i.e., HbA1c or blood glucose). Additionally, a major limitation of previous studies has been the inclusion of participants with cognitive impairment or preclinical dementia in the study populations. AD-related brain and cognitive changes are thought to begin about a decade before dementia is clinically diagnosed (124). It is extremely important to take this into account when investigating which cognitive domains

are impaired early in older adults with diabetes and how this impairment progresses over time. If people with cognitive impairment or preclinical dementia are included in such studies, the observed diabetes-related cognitive deficits or decline may reflect cognitive changes due to causes other than diabetes, such as underlying AD-related degenerative processes. In our studies (I and II), we carefully excluded participants with CIND or incident dementia, and our results showed that cognitive deterioration in people with diabetes may start by affecting fluid abilities (perceptual speed, attention, and executive function), which are also those that decline more rapidly over time. This pattern differs from the typical cognitive progression observed in AD, which is mostly characterized by disturbances of crystallized abilities, particularly of episodic memory (2, 70).

Overall, our results seem to point toward the existence of vascular-related processes in the brain that underlie the early stages of cognitive deterioration in people with diabetes. These results are clinically relevant, as they provide practical guidance about cognitive assessment, especially the tests to be used to detect diabetes-related cognitive deficits early and to monitor their progression. Screening or specific cognitive tests that target fluid abilities—particularly psychomotor speed, attention, and executive function—should be preferred to tests that predominantly assess crystallized abilities (i.e., the MMSE).

**The role of VRFs, CVDs, and *APOE*  $\epsilon$ 4.** CVD and diabetes are often comorbid (125), and VRFs, CVDs, and *APOE*  $\epsilon$ 4 are also risk factors for dementia and for diabetes (3, 126). Thus, it is plausible to believe that these factors might play a role in cognitive dysfunction or decline related to diabetes. As expected, in Study I, smoking, overweight/obesity, and CVDs contributed to the association between diabetes and cognitive deficits (122). Indeed, the negative impact of diabetes on cognitive performance was present in people with diabetes and with VRFs or CVDs. However, these factors did not alter the independent association between diabetes and accelerated cognitive decline observed in Study II. This suggests that VRFs or CVDs can modulate the effect of diabetes on cognitive performance in the initial stages of overt cognitive impairment; however, their role in the cognitive progression linked to diabetes warrants further investigation. Furthermore, our results also showed that the negative impact of diabetes on cognitive performance was present among older adults with diabetes but *APOE*  $\epsilon$ 4 non-carriers; similar results have been described previously (60, 127). A possible interpretation is that *APOE*  $\epsilon$ 4 carriers have already accumulated sufficient AD-related cerebral biochemical and structural pathology to manifest clinically relevant cognitive impairment earlier than non-carriers (124, 127). On the other hand,  $\epsilon$ 4 non-carriers might require additional physiological insults, such as diabetes, to reach the threshold for expressing clinically relevant cognitive impairment (122, 127).

### 5.1.2 Prediabetes and cognitive aging

The associations between prediabetes and cognitive deficits and between prediabetes and cognitive decline have been examined in a few previous cross-sectional and longitudinal

studies (17, 27, 31, 36, 39, 41, 48, 49); no associations were observed. Partially in line with these previous findings, in Study I we found no association between prediabetes and cognitive deficits in specific domains among cognitively intact participants. Conversely, we found an association between prediabetes and baseline poor memory performance in Study II (117). As prediabetes is not a chronic condition, but transitions to normoglycemia or diabetes may occur, we also tested prediabetes as a time-varying exposure and found that its negative association with memory performance was no longer significant. On the other hand, in Study III, prevalent and time-varying prediabetes were associated with faster MMSE decline over nine years than was being diabetes-free. Finally, in Study IV, we found no association between prediabetes and risk of dementia, which is in disagreement with previous findings from the Kungsholmen project (60).

The Kungsholmen project was the forerunner of SNAC-K; it was conducted between 1987 and 2000 and included people  $\geq 75$  years who lived in Kungsholmen. Prediabetes was identified in different ways in the two population-based studies: the Kungsholmen project used RBG, and SNAC-K used HbA1c (60, 122). These methods measure different aspects of prediabetes. Specifically, HbA1c measures the average proportion of hemoglobin proteins bound by glucose over the past three months (128) and as such captures only chronic hyperglycemia, not acute hyperglycemia or fluctuation in glycemic levels. The RBG test measures the concentration of blood glucose at the moment the blood sample is taken. It is therefore likely that observed discrepancies in the findings in the literature and in this thesis reflect methodological differences in the ways prediabetes was assessed. The findings of Rönnekaa et al. (129) are consistent with this hypothesis. They assessed the relationship between different markers of prediabetes and risk of dementia and found that associations differed by type of marker.

Our findings of a possible link between prediabetes and cognitive aging must thus be interpreted with caution. Indeed, future studies are needed to investigate whether and to what extent different aspects of glucose metabolism (hyperglycemia itself or hyperglycemia secondary to insulin-resistance) in the prediabetic stage are linked to the different cognitive outcomes.

### **5.1.3 The role of an active lifestyle and rich social network in diabetes-related dementia**

The results of Study IV showed that active engagement in leisure activities and a rich social network significantly diminished the risk of dementia that was related to diabetes. These results suggest that an active and socially integrated lifestyle might counteract the risk effect of diabetes on dementia.

Leisure activities and social network are among the major components of healthy lifestyle behaviors in older adults. With advancing age, people may tend to engage less in socially,

mentally, and physically challenging activities. However, an active lifestyle and staying socially integrated is particularly important in old age.

Leisure activities are activities that people engage in for enjoyment or well-being during their free time. In other words, they are activities independent of work or outside people's daily routines (130). Numerous previous population-based studies have reported that older people who are highly engaged in physical, mental, or social leisure activities have a decreased risk of cognitive impairment (130) and dementia (3, 118, 131-134). Similarly, intervention studies have shown that enhancing leisure-time physical activity substantially reduces the risk of diabetes in at-risk adults (135-137). However, those studies focused mostly on the physical component of leisure activities, neglecting the mental and social components.

Social network has been defined as the network of social relationships surrounding a person. It therefore includes the person's social connections, activities, and social support (138). Previous studies have found that different aspects of social networks (e.g. network size, satisfaction, support) reduce the rate of cognitive decline (139, 140) or risk of dementia (141-145), although other studies have not found such links (146, 147). Furthermore, a rich social network has been associated with a decreased risk of developing diabetes, better glycemic control, and better diabetes self-management (148, 149).

Previous studies have addressed the relationship between lifestyle behaviors and risk of dementia or lifestyle behaviors and risk of diabetes. However, no previous epidemiological study seems to have investigated the combined counteracting effect of an active lifestyle and rich social network on the risk of diabetes-related dementia. Currently there is no pharmacological treatment for dementia. Thus, a lot of effort is devoted to identifying strategies that may help prevent dementia. In this context, our results are of particular importance because they suggest that a sizeable proportion of diabetes-related dementia could be delayed by engaging in an active lifestyle; that is, by being highly engaged in leisure activities and having a rich social network. Future behavioral interventions should aim to understand the extent to which an active lifestyle counteracts the risk of dementia in older adults with diabetes.

#### **5.1.4 Biological mechanisms**

**Cerebral vascular mechanisms.** In Study III, diabetes was associated with larger WMHV at baseline and a faster increase in WMHV during follow-up. Prediabetes was also related to smaller global brain volume, a finding that mostly reflected smaller white matter volume. No association was observed between prediabetes or diabetes and hippocampal volume, an AD-related degenerative marker. Together, these findings suggest that diabetes may affect the brain primarily through vascular pathway linked to the accumulation of cerebral microvascular lesions. Also, these vascular brain alterations may already exist in the prediabetic stage.

WMHs, a sign of SVD, are probably due to progressive demyelination and axonal loss that leads to substantial white matter loss and brain atrophy over time, thus contributing to the accumulation of brain damage (87). WMH can also contribute to cognitive decline and dementia in old age (86, 150, 151). As summarized in the introduction of this thesis, the link between diabetes and the progression of WMH has been addressed in four previous prospective studies, which reported no differences in the rate of WMH changes in people with diabetes vs. people who were diabetes-free (81-84). Differences in study design (population-based vs. clinic-based), characteristics of the study sample (demographics, methods used to identify prediabetes, sample size), or longer follow-up might explain the discrepancies between our and previous findings.

Diabetes and prediabetes can affect the brain through the oxidative stress-related or inflammatory pathways that stem from chronic hyperglycemia (152). Hyperglycemia may trigger or exacerbate age-related oxidative stress and inflammatory processes (153). These, in turn, lead to dysfunction or disruption of the blood-brain barrier (BBB), damaging the microvasculature of the brain over time (154). Compromised BBB integrity is a key component in SVD-related changes in white matter (88). Neuroimaging and postmortem studies have reported changes in BBB permeability in patients with SVD and found BBB leakage in areas of white matter lesions (88). Furthermore, a recent animal study found a breakdown in the BBB of diabetic mice (154). In particular, the authors observed changes in pericytes and astrocytes, cells responsible for maintaining BBB integrity and that are part of the neurovascular unit (155).

Our results do not rule out the possibility that in people with diabetes, cerebrovascular-related degeneration may overlap with AD-related degeneration in the more advanced stages of cognitive decline. Indeed, the participants in the MRI sample were relatively healthy and had a high cognition function at baseline (their mean MMSE score was 29). If these people were in cognitive decline, they were likely in its initial stages, as further supported by the minimal but statistically non-significant differences in the rate of cognitive decline over follow-up in the participants with diabetes and those without (see manuscript III). Additionally, previous studies have reported that diabetes is related to an increased risk of AD (59, 156, 157), and the majority of dementia cases have mixed vascular and AD-related neuropathology (65, 158). Unexpectedly, in our SNAC-K sample, we found no association between diabetes and AD. Future studies could focus on the question of whether cognitive decline in people with diabetes initially occurs through the vascular pathway and later overlaps or interacts with separate neuropathology related to AD. If such overlap or interaction is observed, the studies could seek to identify the stage of cognitive aging at which the overlap or interaction begins.

**Cognitive reserve.** The theory of cognitive reserve stems from the numerous epidemiological studies showing that dementia risk is reduced in older people who were exposed to certain factors over the course of their lives, such as a high level of education, complex occupation(s), or an active lifestyle (159, 160). The theory attempts to explain the discrepancies between the person's relatively preserved cognitive performance and brain

pathology levels typically associated with the impaired cognitive performance (159). According to the cognitive reserve theory, the experiences accumulated during the lifespan help shape the person's neuronal activity and networks, improving the person's cognitive efficiency, capacity, and flexibility or providing new compensatory cognitive networks that can be used during brain changes (159). It follows that older people with high cognitive reserve will cope better with brain pathology by using preexisting neuronal reserve or activating compensatory networks to maintain their cognitive performance (159, 161). Our finding that an overall active lifestyle and rich social network may substantially reduce the risk of diabetes-related dementia can be explained in terms of cognitive reserve. Social networks prompt people to interact by engaging in verbal and nonverbal communication, thus helping to maintain cognitive abilities in old age. Similarly, leisure activities challenge people mentally, physically, and socially. An active and socially integrated lifestyle may therefore help older adults with diabetes to keep their cardiovascular and brain health, preserving their brain chemistry, structure, and function. This would help people with diabetes to maintain their brain capacity by resisting ongoing vascular-related brain changes (162) or activating compensatory networks to cope with the underlying neurovascular pathology and maintain their cognitive performance level (161).

## **5.2 METHODOLOGICAL CONSIDERATIONS**

### **5.2.1 Study design**

All studies in this thesis were longitudinal, population-based, observational studies, except Study I, which was cross-sectional. In cross-sectional studies, exposures (diabetes) and outcomes (cognitive performance) are observed simultaneously at a specific point in time (baseline assessment), preventing the establishment of a temporal relationship between the two. Additionally, cross-sectional studies assess differences in the outcome between two or more groups of individuals (interindividual variability), which makes it difficult to rule out possible intraindividual effects, such as those related to cohort differences in people of different ages (163).

With regard to the sources of the study populations, both SNAC-K and SATSA had few exclusion criteria (e.g., age <60 or <50; inability to speak Swedish). Furthermore, as consequence of the recruitment strategies (random sampling of 11 age-cohorts in SNAC-K and from the Swedish Twin Registry in SATSA), the study samples can be considered representative of the population living in Kungsholmen (SNAC-K) or in Sweden (SATSA).

### **5.2.2 Sources of errors**

One of the aims of epidemiological studies is to obtain valid and precise estimates (estimates with little error) of the effect of an exposure on an outcome. There are two main types of



error in observational studies: 1) systematic error, or bias, related to the way the study was conducted (selection of the study population, measurement of variables, control for potential confounders) and 2) random error, the random variability that is left after the systematic error has been addressed and that is thus difficult to predict (164).

**Systematic error (lack of internal validity).** Systematic errors or bias can be classified in three broad categories: selection bias, which includes attrition; information bias; and confounding.

- 1) **Selection bias.** Selection bias is a distortion in the association between the exposure and outcome that is linked to the procedure used to select the study sample. Selection biases can arise when only certain people in an initially randomly selected group choose to participate in a study, and those people share specific characteristics. For instance, the people who chose to participate in SNAC-K or SATSA might have been generally healthier (cognitively and physically) than those who declined to participate; this phenomenon is called the healthy respondent effect. In SNAC-K, the 1227 people who declined to participate in the baseline survey were more likely to die shortly after the beginning of the study than those who chose to participate (165), which supports the hypothesis that participants were potentially healthier than those who declined to participate. Similarly, we compared the baseline characteristics of participants and non-participants in the SNAC-K MRI sample. Overall, participants in the MRI sample were younger, relatively healthier, and had better cognitive function than those who were not scanned. The use of self-selected healthier participants therefore might have lead to an underestimation of the effect of the exposure on the outcomes. Unfortunately, in SATSA was not possible to quantify the healthy-respondent effect because health-related data were only available for people who agreed to participate.

Additional selection bias may have come from values missing because of non-response (dropouts) and attrition (death). In studies II through IV, we used multiple imputation to understand how data missing because of drop-out would have affected the observed associations. The results of these secondary analyses showed associations similar to those found in the initial analyses. We also investigated the potential impact of attrition on our results. The attrition rates in SNAC-K varied between nearly 24% (over six years) and 26% (over 10 years), which is quite low; in SATSA, the attrition rate was about 45% over 23 years. To understand how the attrition affected our results, in studies II to IV, we compared the baseline characteristics of those who participated and those who died. Those who died were less healthy overall (they had worse cognitive and physical function) than participants. The differences in baseline characteristics between participants and those who died in SNAC-K were similar to those observed in SATSA. Therefore, in this scenario, sample selection probably led to a more advantaged study population and thus an underestimation of the negative effect of prediabetes and of diabetes on cognitive outcomes.

2) **Information bias.** Information biases can arise from the measurements used to collect information about or from people (166). For categorical variables, measurement error can lead to assign the person to an incorrect category, therefore the person is misclassified. Exposures, outcomes, and other variables can be misclassified in two ways:

- “Non-differential” misclassification results from the degree of inaccuracy in the methods used to collect the data (random error). It occurs when different groups (e.g., exposed and unexposed) have the same probability of being misclassified, independently of other variables. Non-differential misclassification is of interest in both the exposure and the outcome; therefore, in this thesis, this type of misclassification would have arisen from the assessment of diabetes, prediabetes, cognitive outcomes, or dementia.
- “Differential” misclassification is related to systematic error. It occurs when different groups (e.g., exposed and unexposed) have different probability of being (mis)classified depending on the person’s disease/status. For example, differential misclassification would occur if the exposure were more likely to be misclassified for people with than those without the outcome.

**Ascertainment of exposure.** Non-differential misclassification of the exposures (i.e., prediabetes and diabetes) is a potential source of information bias. The recommended standard diagnostic tests for detecting diabetes and prediabetes are based on HbA1c or blood glucose levels—either FBG or an oral glucose tolerance test (measuring blood glucose 2 hours after drinking 75 g of glucose) (98). SNAC-K used the HbA1c test to identify diabetes (including undiagnosed diabetes) and prediabetes, and SATSA used the FBG or RBG test. The concordance between these tests is imperfect, partly because of the intrinsic limitations of the tests and partly because they measure different markers of hyperglycemia. Indeed, HbA1c measures the average proportion of hemoglobin proteins bound by glucose over three months prior to the blood test (128). As such, it is likely to capture the chronic hyperglycemia but not acute hyperglycemia or fluctuations in glycemic level. The HbA1c test has several advantages: unlike the tests that measure blood glucose levels (i.e., FBG, RBG, and oral glucose tolerance), fasting is not needed, and the HbA1c test is less vulnerable than the others to day-to-day variability due to stress or illness (98). Some studies show that HbA1c is less sensitive than FBG and oral glucose tolerance in detecting people with diabetes or impaired glucose tolerance (137, 167, 168), but one other study did not find such a difference in sensitivity (169). It follows that in our samples, some prediabetes or diabetes cases might have been misclassified, leading to a dilution of the observed associations. Therefore, even if there is an association between prediabetes or diabetes and cognitive outcomes, we might not have detected it or we might have underestimated its magnitude.

**Ascertainment of outcomes.** Non-differential misclassification of the outcomes is another potential source of information bias. In studies I and II, cognitive function was measured

with composite scores from neuropsychological tests. These scores have the advantage of increasing reliability and reducing measurement error (i.e., ceiling/floor effects) (117, 122). However, in Study III, prediabetes- and diabetes-related cognitive decline was assessed with the MMSE. Although the MMSE has numerous advantages, this cognitive screening test also has several limitations. First, the MMSE has both ceiling and floor effects: the higher scores do not necessarily reflect complete absence of cognitive impairment, and the lower scores do not necessarily reflect the absolute presence of severe impairment (170). Second, the MMSE lacks items that assess processing speed and attention/executive function that seems to be affected early by diabetes. As consequence, the MMSE may not be sensitive enough to detect subtle cognitive changes in the early phase of cognitive impairment, particularly among well-educated adults such as the SNAC-K participants. These intrinsic limitations of the MMSE could have led to underestimating or not detecting the effect of prediabetes or diabetes on cognitive decline. However, MMSE scores correlate well with several global brain measurements (171), which were the main focus of study III.

Differential classification can also occur when only self-reported information is used to assess a variable. For example, the probability of recalling relevant information may be different in people who develop dementia and those who do not. In Study IV, participants without incident dementia might have reported more accurate information on leisure activities and social network because their memory functioned well, whereas participants with incident dementia might forget them and report less accurate information. In this case, the observed effects of active lifestyle on dementia risk might have been underestimated or overestimated. After excluding participants who developed incident dementia between baseline and the first follow-up and/or who had an MMSE score  $\leq 27$ , the associations were unchanged. Finally, differential misclassification might have arisen from using other self-reported information to identify, for example, medical conditions. To avoid differential misclassification of medical conditions, self-reported information was not the only kind used; we also obtained information on medical conditions from other sources, including registries, physician examination, and participants' proxies. Additionally, in all studies, we either excluded participants with dementia in the main analysis or in secondary analysis. The results of such secondary analyses were similar to those of the initial analyses.

- 3) **Confounding.** A confounder is a known risk factor for the outcome that is associated with but not caused by the exposure (if it were caused by the exposure, it would be a mediator) (172). When the effect of the exposure on the outcome is mixed with the effect of other variables on the outcome, the final effect of the exposure will either be overestimated or underestimated. We considered the major known confounders in all our analyses by adjusting the statistical models for these factors (e.g., demographics, VRFs, CVDs, *APOE*  $\epsilon 4$ ). Additionally, for confounding to occur, the distribution of the third variable in the strata of the exposure should differ. Therefore, in each study, we tested for possible interactions (additive and multiplicative) between the exposure and possible confounders

in predicting the outcomes and performed stratified analyses. However, although various exposure and potential confounders were considered in this thesis, as in all epidemiological studies, unmeasured confounding due to unknown factors could still have occurred.

**Possible reverse causality and critical periods.** Two main challenges in research on the determinants of cognitive aging and dementia are: 1) the possibility of reverse causation and 2) the critical periods or time windows in which the exposure exerts a risk effect on the outcome. Reverse causality occurs when the outcome causes the risk factor rather than vice versa. Therefore, it is important to consider whether the exposure really came before the outcome or the outcome (e.g., dementia) may have started to develop before the exposure (173). Specifically, in this thesis, given that the preclinical phase of dementia can begin about 20 years before clinical diagnosis (5), the observed associations between diabetes and cognitive outcomes (cognitive deficits, decline, brain changes, and dementia) might be attributable to preclinical dementia rather than to diabetes itself. We attempted to control for potential reverse causality by excluding people with CIND at baseline, who developed dementia over follow-up, and/or including only participants with MMSE score  $\geq 28$  (in the main or supplementary analyses). Another important issue to consider in research on diabetes and cognitive aging research is the critical time windows when prediabetes and/or diabetes occur (midlife, late-life, or changes over time) and their impact on cognitive decline. In SATSA and SNAC-K, repeated measures of diabetes (at different ages) were available, which provided the opportunity to test whether time-invariant and time-varying prediabetes or diabetes affected cognitive decline differently.

**Random error.** Major sources of random error are related to population sampling and to measurement (164). The ideal way to investigate a phenomenon (such as the relationship between diabetes and cognitive aging), would be to investigate it in the whole population. However, in the real world, this is not possible. Instead, during the sampling process, we select a random sample that is representative of the population of interest and calculate sample statistics and estimates (e.g., mean, SD, median,  $\beta$ -coefficients, HR). The random error due to the sampling procedure can be reduced by increasing the sample size. Random errors can also occur because of the limited precision of devices, tools, and/or methods used to measure the exposure (e.g., laboratory techniques used to measure HbA1c), the outcome (e.g., cognitive tests), or other variables. Random error due to measurement errors can be minimized by collecting and averaging several measurements of the same variable.

### 5.2.3 Generalizability or external validity

Epidemiological studies attempt to use randomly selected samples from a broader target population. The random sample should be representative of the study sample. That is, it should share the same characteristics as the target population. This is because the ultimate

goal of observational studies is to generalize what is observed in the random sample to the larger targeted population. Nevertheless, systematic errors (e.g., selection and information bias, confounding) may lead to incorrect estimates of the association between exposure and outcome, compromising the generalizability of the findings. When we draw conclusions from any epidemiological study, we must keep in mind that no study population can be fully representative of all other populations because every study population has unique characteristics.

**SNAC-K.** Participants in SNAC-K live in Kungsholmen, a neighborhood in central Stockholm. SNAC-K participants have high levels of education and are relatively healthy and wealthy (174, 175). This possible selection bias might have led to an underestimation of the observed associations. Consequently, the effect of diabetes on different stages of cognitive aging found in this doctoral project can be generalized to the entire population of older adults, independent of their unique characteristics. However, the magnitude of the observed effects would vary according to the unique characteristics of the populations. Thus, the magnitude of the observed effects can be generalized only to populations with characteristics similar to those of the SNAC-K population.

**SATSA.** SATSA included twins living all over Sweden who were reared apart from each other and a matched sample of twins brought up together. A common criticism of twin studies is that results from twins might not be applicable to non-twins, which would mean that the results of twin studies were not generalizable to the wider general population. However, previous studies have shown that the twins in the Swedish Twin Registry are much like the people in the general Swedish population (176). Additionally, in our SATSA-based study, we controlled the analyses for the fact that twins are individuals who are genetically related. We did this by adding two random effects, each of which included a random intercept and a random slope for age: one for the person-specific identifier and one for the twin-pair identifier. We are thus confident that the results of Study II can be generalized to the general population of non-twins.



## 6 CONCLUSIONS

- I. In cognitively intact older adults, diabetes was cross-sectionally associated with poorer performance in fluid abilities, in particular in perceptual speed, category fluency, and attention/primary memory tasks. These associations were present in older adults with diabetes and VRFs (smoking or overweight/obesity) or CVDs and in *APOE*  $\epsilon 4$  non-carriers. In sum, the results suggest that fluid abilities can be affected by diabetes early in the process of cognitive deterioration. Moreover, diabetes may not be the sole factor contributing to the observed cognitive deficits.
- II. Longitudinally, diabetes accelerated cognitive decline in perceptual speed and verbal abilities, independently of VRFs, CVDs, and the *APOE*  $\epsilon 4$  allele. Although people with prediabetes had poorer baseline memory performance than those who were diabetes-free, memory function in those with prediabetes declined less steeply over time.
- III. Prediabetes and diabetes were associated with accelerated global cognitive decline. At the structural brain level, prediabetes was associated with smaller total brain volume, particularly white matter volume, but only at baseline. WMH accumulated faster over time in those with diabetes than those who were diabetes-free. The results suggest that microvascular processes may play a fundamental role in prediabetes- and diabetes-related cognitive decline.
- IV. Diabetes was associated with an increased risk of dementia, particularly of vascular origin, whereas the association between prediabetes and dementia was not evident. However, higher engagement in mental, physical, and social leisure activities and/or having a rich social network could significantly counteract the detrimental effect of diabetes on dementia.





## 7 RELEVANCE AND IMPLICATIONS

Today's epidemic of diabetes and dementia is without precedent, and the number of people with each of these two diseases is expected to double, even triple, in the next three decades as the older population continues to grow (4, 11). Consequently, both diseases will pose critical challenges to health care systems around the world, becoming two of the largest public health emergencies of the twenty-first century.

The onset of dementia occurs nearly two decades before clinical diagnosis, and several cardiometabolic risk factors contribute substantially to its onset in late life (5, 7). Indeed, diabetes is one of the seven main causes of dementia (7). Currently, there is no cure for dementia, but preventing it by postponing the symptoms seems achievable (3, 177).

Promising findings from epidemiological studies suggest that an active lifestyle might provide sufficient cognitive reserve to enable people to cope with accumulating lesions in the aging brain, including AD-related pathology. In this scenario, the most effective strategy for preventing dementia (i.e., reducing or delaying symptoms) in people with diabetes could be preventing cardiometabolic diseases through combined pharmacological and multidomain lifestyle/behavioral interventions.

The findings of this thesis have relevant clinical implications. First, understanding cognitive trajectories and the different combinations of modifiable risk factors may help with the early identification of people with diabetes who are at risk of dementia. This, in turn, will allow for timely initiation of preventative strategies (such as individually tailored interventions), thus delaying progression to dementia. Second, although our understanding of the pathophysiology of AD has advanced considerably in the last twenty years, thus far, clinical trials of new disease-modifying drugs have failed to produce meaningful and long-lasting cognitive improvements (178). A reason the traditional treatment options for AD might be inadequate—and one that might partly explain the failure of clinical trials—could be that the trials targeted the wrong people (e.g., those with mixed dementia rather than pure AD) and perhaps provided the intervention at the wrong time (e.g., too late). Indeed, dementia is a multifactorial disease, and AD is only one of the causes. Mixed pathologies (vascular and AD-neurodegenerative) lie behind most cases (158). Future clinical trials therefore need to include the right participants (e.g., pure AD) and take into account the potential overlapping etiology of most dementia cases. With this in mind, it is possible that interventions based on the combination of different therapeutic approaches (drugs and lifestyle change) that address multiple targets (e.g., cardiometabolic health and AD-related pathology) could be effective future strategies for preventing dementia in people with diabetes.



## 8 FUTURE DIRECTIONS

This doctoral thesis built on and extends the existing literature on diabetes and cognition. The results add another piece to the puzzle about how prediabetes and diabetes impact different degrees of cognitive function during cognitive aging. However, to complete the puzzle, we need more long-term longitudinal studies that integrate data from comprehensive neuropsychological batteries with data on AD-related and vascular biomarkers—for example, from neuroimaging, cerebrospinal fluid, or blood (e.g., A $\beta$ -plaque, tau, inflammatory cytokines, or oxidative stress markers).

To improve the process of predicting and diagnosing dementia as well as the outcomes of clinical trials, further steps are needed. First, we should map the cognitive profiles of the different brain pathologies (pure AD, vascular dementia, and mixed dementia) in people with diabetes. In particular, we need to understand whether and to what extent the cognitive characteristics of older adults with pure AD, vascular dementia, or mixed pathologies differ in the different stages of cognitive aging (from intact cognition, through cognitive decline, to cognitive impairment and dementia). Second and equally, we need to understand the trajectories of systemic, biochemical, cerebral, and cognitive markers in the cognitive profiles that characterize the different brain pathologies. Third, given the symbiotic relationship between the brain and the heart and the clustering of diabetes with other cardiometabolic conditions (hypertension, overweight/obesity, and heart disease), we also need to address the combined contributions of these cardiometabolic conditions to cognitive and brain deterioration. Fourth, considering the discrepancies in the findings on this topic, future studies on the link between prediabetes and cognitive aging need methodological improvements, particularly in the markers they use to assess prediabetes. Fifth, further investigation is warranted into the details of the possible neuroprotective role of cognitive reserve (and other related concepts such as brain maintenance) over the entire life course. It is possible that different factors (e.g., education, occupational complexity) related to cognitive reserve may interact in complex ways over time to build up this reserve and thus protect people with prediabetes or diabetes from developing dementia. Finally, the findings of this thesis can be useful in designing multidomain intervention that explore whether and to what extent the combination of hypoglycemic drugs and lifestyle modification can delay the progression to dementia in people with diabetes.



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## 11 APPENDICES

### 11.1 SUMMARY OF THE CROSS-SECTIONAL AND CASE-CONTROL STUDIES ON THE RELATIONSHIP BETWEEN PRE/DIABETES AND COGNITIVE DEFICITS

Reference	Study population	Prediabetes	Diabetes	Cognitive domains	Results	Covariates
Geijselaers et al. 2017 (17) Netherlands	Population-based n=2531 Mean age 60 yrs.	OGTT 7.8-11.0 mmol/L	Medication use OGTT $\geq 11.1$ mmol/L	Composite from z-scores: Memory Processing speed Attention/executive	Diabetes had poor performance in all domains.  No association for prediabetes	Age, sex, education
Fink et al. 2017 (179) Germany	Population-based n=1299 with MMSE $\geq 24$ Median age 54.4 yrs.	No	Medication use HbA1c $\geq 6.5\%$ FBG $\geq 126$ mg/L OGTT $\geq 200$ mg/L	Composite score for global cognition from CERAD-battery	Increased odds of poor cognitive function	None
Tuligenga et al. 2014 (27) UK	Population-based n=5183 dementia-free Median age 54.4 yrs.	FBG 6.1-7.0 (non-fasting <7.0) mmol/L and OGTT <7.8 (non-fasting 7.8-11.1) mmol/L	FBG $\geq 7.0$ mmol/L OGTT $\geq 11.1$ mmol/L	Composite from z-scores: Global score Memory Reasoning Phonemic fluency Semantic fluency	Diabetes had poor performance in reasoning.  No association for prediabetes	Age, sex, education, marital status, VRF, diet, CVDs, hypertension, respiratory disease, cholesterol, antidepressant, lipid-lowering drugs
Köhler et al. 2012 (26) Germany	GP-based n=3327 dementia-free Aged $\geq 75$	No	Self-report	Single cognitive tests: • Immediate/delayed recall • Verbal fluency	Poor performance in executive function	Age, sex, education, living alone, CVDs, hypertension, depressive symptoms, medication



Vicario et al. 2012 (28) Argentina	Population-based n=1365 dementia-free Aged ≥18	No	FBG ≥126 mg/L	MMSE (global cognition) Single cognitive tests: • Benton orientation questionnaire • Boston Naming test • Clock Drawing test • Alternating series test	Poor performance in global cognition (MMSE and Benton) and executive function (clock and alternating series)	None
van den Berg et al. 2010 (29) Netherlands	Clinical-based case-control n=106 (68 diabetes) dementia-free Aged 56-80	No	Physician-report	Composite from z-scores: Memory Attention/executive Abstract reasoning Visuo-constructional Speed	Poor performance in speed and attention/executive function	Age, sex, education, estimated IQ
Arvanitakis et al. 2010 (18) USA	Population-based n=3350 dementia-free Aged 43-70	No	Self-report Medication use	Composite from z-scores: Episodic memory Semantic memory Working memory Visuospatial Speed	Poor performance in semantic memory	Age, sex, education, race
Yeung et al. 2009 (32) Canada	Population-based n=465 dementia-free Aged 53-90	No	Self-report Medication use Medical records	MMSE (global cognition) Single cognitive tests: • Immediate/delayed recall; Story (episodic memory) • Vocabulary; Fact recall (semantic memory) • Opposite; Figure of speech; Similarities (verbal fluency) • Hayling; Brixton Spatial Anticipation; Stroop (executive function) • Five speed tests (speed)	Poor performance in speed and executive function	None

Ruis et al. 2009 (19) Netherlands	Case-control n=252 (183 diabetes) dementia-free Aged 50-70	No	Self-report Medication use FBG $\geq 7.1$ mmol/L RBG $\geq 11.1$ mmol/L OGGT $\geq 11.1$ mmol/L	Composite from z-scores: Memory Attention/executive Abstract reasoning Visuo-construction Language comprehension Processing speed	Poor performance in memory	Age, sex, education, IQ
Maggi et al. 2009 (30) Italy	Population-based n=3037 Aged $\geq 65$	No	Self-report Medication use Medical records FBG $\geq 140$ mg/dl	MMSE (global cognition) Single cognitive tests: • Story immediate/delayed recall (episodic memory) • Attentional matrix (attention)	Poor performance in MMSE and attention among women but not men	Age, sex, education, BMI, CVD, hypertension, parkinsonism, neuropathy, depressive symptoms
Okereke et al. 2008 (20) USA	Population-based n=12233 Aged $\geq 65$	No	Self-report	TICS (global cognition) Single cognitive tests: • Immediate/delayed recall; TICS-recall (memory) • Category fluency (verbal fluency)  Composite from z-scores: Global cognition Memory	Poor performance in TICS and memory among men and women	Age, education, VRFs, high blood pressure, high cholesterol, physical activity, depression, (postmenopausal hormone use in women).
Saczynski et al. 2008 (31) Iceland	Population-based n=1917 Aged $\geq 65$	FBG 5.6-6.9 mmol/L	Self-report Medication use FBG $\geq 7.1$ mmol/L	Composite from z-scores: Memory Executive function Processing speed	Diabetes: poor performance in executive function and speed  No association for prediabetes	Age, sex, education, VRFs, hypertension, <i>APOE</i> $\epsilon 4$ , myocardial infarction, cholesterol, white matter lesions load, visual acuity, insulin level

van Harten et al. 2007 (42) Netherlands	Clinical-based case-control n=136 (92 diabetes) Aged ≥60	No	Medical records	Composite from z-scores: Global cognition Executive function Mental speed Motor speed	Poor performance in executive function and speed tasks	Age, sex, education, hypertension
Brands et al. 2007 (21) Netherlands	Clinical-based case-control n=174 (119 diabetes) Aged 56-78	No	Medical records	Composite from z-score: Memory Attention/executive Abstract reasoning Visuo-construction Processing speed	Poor performance in memory, attention/executiv e function, speed	Depression
van den Berg et al. 2006 (33) Netherlands	Population-based n=596 Aged 85-90	No	Medical records Medication use	MMSE (global cognition) Single cognitive tests: • Immediate/delayed recall (memory) • Stroop test (attention/executive) • Letter Digit Coding (speed)	Poor performance in speed and attention/executive	Sex, education
Debling et al. 2006 (35) Germany	Population-based n=740 Aged ≥70	No	Self-reported Medication use	TICS (global cognition) Immediate/delayed recall (memory)	Poor TICS performance	Age, sex, education, VRF, physical exercise, depressive symptoms
Arvanitakis et al. 2006 (22) USA	Population-based n=882 dementia-free Mean age 80 yrs.	No	Self-reported Medication use	Composite from z-score: Episodic memory Semantic memory Working memory Perceptual speed Visuospatial ability	Poor performance in semantic memory and speed	Age, sex, education
Kumari et al. 2005 (38) UK	Population-based n=5183 dementia-free Median age 54.4 yrs.	No	Self-reported FBG ≥7.0 mmol/L OGTT ≥11.1 mmol/L	Single cognitive tests: • Word free recall (memory) • Alice Heim 4 (reasoning) • Phonemic fluency • Semantic and semantivc fluency (verbal) • Mill Hill (language)	Poor performance in reasoning and language	Age, employment grade

Kanaya et al. 2004 (48) USA	Population-based n=999 Aged 42-89	OGTT 140-199 mg/dL	Self-reported FBG $\geq 126$ mg/dL OGTT $\geq 200$ mg/dL	MMSE (global cognition) Single cognitive tests: • Verbal fluency • Trail Making Test-B (attention/executive)	No association for diabetes or prediabetes	Age, education, depressive symptoms, <i>APOE</i> $\epsilon 4$ (estrogens in women)
Yaffe et al. 2004 (41) Multicenter	Population-based n=7027 women Aged >60	FBG 6.1-7.0 mmol/L	Self-reported Medication use FBG $\geq 7.0$ mmol/L	Single cognitive tests: • Word list recall (memory) • Word fluency (semantic memory) • Trail Making Test-A, B (attention/executive)  Composite z-score for global cognition	Pre- plus diabetes: poor performance in Trail A and recall task, and global cognition.	Age, education, race, depression
Hassing et al. 2003 (23) Sweden	Population-based n=338 Aged 80-93	No	Medical records FBG $\geq 6.7$ mmol/L	MMSE (global cognition) Single cognitive tests: • Prose recall, Thurstone's Picture Memory, Memory-in- Reality (episodic memory) • Information Task, Verbal Meaning test (semantic memory) • Digit Span test (short-term memory) • Symbol-Digit Substitution & Perceptual speed test (speed) • Koh's Block Design, Clock Test (visuo-spatial) • Figure Logic task (reasoning)	Poor performance in all cognitive tests.	None
Nilsson et al. 2002 (180) Sweden	Population-based n=392 dementia-free Aged $\geq 75$	No	Self-reported Medication use Inpatient registry RBG >6.0 mmol/L	MMSE (global cognition)	Poorer MMSE performance	Age, sex, education, CVDs, hypertension

Wahlin et al. 2002 (24) Sweden	Population-based n=338 dementia-free Aged ≥75	No	Self-reported Medication use Inpatient registry RFBG >6.0 mmol/L	Single cognitive tests: • Episodic word recall (memory) • Verbal fluency	Poorer performance in memory and letter fluency	Age, sex, education, CVDs
Asimakopoulou et al. 2002 (25) UK	Clinical-based case-control n=66 (33 diabetes) Aged ≥39	No	Self-reported Medical records	Single cognitive tests: • DSST (speed) • Digit Span; Logical Memory A, B; Implicit memory (memory) • Trail Making Test-A, B (executive function)	Poorer performance in tasks of episodic and working memory	Age, premorbid IQ, BMI, depression
Fontbonne et al. 2001 (36) France	Population-based n=961 with MMSE>26 Aged 59-71	FBG 6.1-7.0 mmol/L	Self-reported FBG ≥7.0 mmol/L	MMSE (global cognition) Single cognitive tests: • Immediate recall; Benton Visual Retention (memory) • Trail Making Test-B; PASAT (attention/executive) • Facial Recognition (visuospatial/attention) • Raven's Matrices (Reasoning) • DSST; Finger Tapping (speed)	Diabetes: Poorer performance in speed tasks.  No association for prediabetes	Age, sex, education
Lindemann et al. 2001 (39) USA	Population-based n=883 dementia-free, aged ≥65	FBG 6.1-7.0 mmol/L OGTT 7.8-11.1 mmol/L	Medication use FBG ≥7.0 mmol/L OGTT ≥11.1 mmol/L	MMSE Single cognitive tests: • Fuld Object Memory Evaluation (memory) • Digits forward (attention/memory) • Clock test (visuoconstruction) • Trail Making Test (executive function)	No association for diabetes or prediabetes	Age, sex, education, ethnicity, depression

Cosway et al. 2001 (34) Scotland	Clinical-based case-control n=76 (38 diabetes) Aged 40-75	No	Medical records HbA1c $\geq 6.5\%$	Single cognitive tests: • Wechsler Memory Scale; Words immediate and delayed recall (memory) • Raven's Matrices (reasoning) • Verbal fluency • Reaction time; Inspection time and Visual change detection (speed)	No association.	Age
Grodstein et al. 2001 (37) USA	Population-based n=1374 women Aged 70-78	No	Self-reported Medical records Medication use	TICS (global cognition) Single cognitive tests: • Boston naming test (memory) • Verbal fluency	Poorer TICS performance	Age, education, vitality index, blood pressure, BMI, use of vitamin E, antidepressant, postmenopausal hormones
Sinclair et al. 2000 (181) UK	Population-based case-control n=789 (396 diabetes) dementia-free Aged $\geq 65$	No	Medical records Medication use FBG $\geq 6.5$ mmol/L	MMSE (global cognition) Clock test	Poor performance in all tests	Age, sex, school-leaving age, occupation, VRFs
Ryan et al. 2000 (40) USA	Population-based case-control n=100 (50 diabetes) Aged 34-65	No	Medical records	Composite from factorial analysis: Learning Memory for stories Problem-solving Psychomotor speed	No association	Age, sex, race, Information task

Abbreviations: *APOE*  $\epsilon 4$ , apolipoprotein E gene- $\epsilon 4$  allele; BMI, body mass index; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CVD, cardio- and cerebrovascular disorders; DSST, digit symbol substitution; FBG, fasting blood glucose; GP, general practitioner; HbA1c, glycated hemoglobin; IQ, intelligence quotient; mmol/L, millimoles per liter; MMSE, Mini-Mental State Examination; OGTT, oral glucose tolerance test; PASAT, Paced Auditory Serial Addition Test; RBG, random blood glucose; TICS, Telephone Interview for Cognitive Status; VRF, vascular risk factors.

## 11.2 SUMMARY OF THE LONGITUDINAL STUDIES ON THE RELATIONSHIP BETWEEN PRE/DIABETES AND COGNITIVE DECLINE

Reference	Study population	Follow-up	Prediabetes	Diabetes	Cognitive domains	Results	Covariates
Palta 2017 USA (56)	Population-based n=3027 dementia-free Aged 72-96	2 waves 7 years	No	Self-reported Medication use	Composite from z-scores: Memory Attention/speed Executive function Visuospatial Language	Faster decline in attention/speed	Age, sex, education, ethnicity, smoking, CVDs, hypertension, depressive symptoms
Demakakos 2017 UK (45)	Population-based n=10524 dementia-free Aged ≥50	6 waves 10 years	No	Self-reported	Single cognitive tests: • Immediate/delay recall (memory) • Verbal fluency	No association	Age, sex, education, marital status, occupation, VRF, CVDs
Sano 2017 USA (57)	Population-based n=7663 dementia-free Aged ≥65	Mean 5 yrs.	No	Medical history	Composite from z-scores: Global Memory Attention/working Language Executive function	Faster decline in global and executive function	Age, gender, ethnicity, site, education, VRF, hypertension, stroke, depression
Rajan 2016 USA (43)	Population-based n=7740 Aged ≥65	4 waves Mean 9 yrs.	No	Medication use Medicare registry	Composite score for global cognition	Faster decline	Age, sex, education, BMI, hypertension, stroke, statin and antihypertensive use
Mayeda 2015 USA (44)	Population-based n=1634 dementia-free Aged ≥60	8 waves 8 years	No	Self-reported Medication use FBG ≥126 mg/L	Short-MMSE (global)	Faster decline	Age, sex, education, abdominal obesity, CVDs, hypertension, depressive symptoms
Rawling 2014 USA (52)	Population-based n=13351 Aged 48-67	3 waves 20 years	No	Self-reported Medication use HbA1c ≥6.5%	Composite from z-scores: Global cognition Memory Executive function Speed	Faster decline in global cognition, executive function, speed	Age, sex, education, center, VRF, CVDs, hypertension, APOE ε4

Mayeda 2014 USA (51)	Population-based n=1886 Aged 48-70	4 waves 14 years	No	Self-reported Medication use FBG $\geq 7.0$ mmol/L RBG $\geq 11.1$ mmol/L	Single cognitive tests: • Delayed recall (memory) • Letter fluency (verbal) • DSST (speed)	Faster decline in verbal fluency and speed	Age, sex, education, waist circumference, hypertension
Tuligenga 2014 UK (27)	Population-based n=5183 dementia-free Median age 54 yrs.	3 waves 10 years	FBG 6.1-7.0 (non-FBG <7.0) mmol/L and OGTT <7.8 (non-fasting 7.8-11.1) mmol/L	FBG $\geq 7.0$ mmol/L OGTT $\geq 11.1$ mmol/L	Composite from z-scores: Global cognition Memory Reasoning Phonemic fluency Semantic fluency	Faster decline in global cognition, memory, reasoning  No association for prediabetes	Age, sex, education, marital status, VRF, diet, CVDs, hypertension, respiratory disease, cholesterol, antidepressant, lipid-lowering drugs
Samaras 2014 Australia (49)	Population-based n=880 dementia-free Aged 70-90	2 waves 2 years	FBG 5.6-6.9 mmol/L	Self-reported Medication use FBG $\geq 7.0$ mmol/L	Composite from z-scores: Global cognition Memory Executive function Visuospatial Language Speed	Faster decline in executive function  No association for prediabetes	Age, sex, education, non-English speakers, VRF, antihypertensive medications, depressive symptoms, <i>APOE</i> $\epsilon 4$
Spauwen 2013 Netherlands (53)	Population-based n=1823 dementia-free Aged $\geq 40$	3 waves 12 years	No	Self-reported Medication use	MMSE (global) Single cognitive tests: • Visual verbal learning (memory) • Concept Shifting (executive function) • Letter Digit Substitution (speed)	Faster decline in memory, executive function, and speed	Age, sex, education, VRF, CVDs, hypertension, depressive symptoms, <i>APOE</i> $\epsilon 4$
Köhler 2012 Germany (26)	GP-based n=3327 dementia-free Aged $\geq 75$	4 waves 4.5 years	No	Self-report	Single cognitive tests: • Immediate/delayed recall • Verbal fluency	No association	Age, sex, education, living alone, CVDs, hypertension, depressive symptoms, medication use



Yaffe 2012 USA (182)	Population-based n=3069, Aged 70-79	4/5 waves 9 years	No	Self-report Medication use FBG $\geq 126$ mg/L OGTT $\geq 200$ mg/dL	Short-MMSE (global) DSST (speed)	Faster global decline	Age, sex, education, race
Wessels 2011 USA (54)	Population-based n=1702 dementia-free Aged $\geq 65$	6 waves 15 years	No	Self-report Medication use	Community Screening Interview for Dementia	Faster decline	Age, sex, education, dementia family history, CVDs, hypertension, depression
Nooyens 2010 Netherlands (55)	Population-based n=3350, aged 43-70	2 waves 5 years	No	Self-reported GP-reported RBG $\geq 11.1$ mmol/L	Composite from z-scores: Global cognition Memory Cognitive flexibility Speed	Faster decline in global cognition, memory, flexibility (in 60+ yrs.)	Age, sex, education, physical activity, VRF, metabolic syndrome factors, myocardial infarction
van den Berg 2010 Netherlands (29)	Clinical-based case-control n=106 (68 diabetes) dementia-free Aged 56-80	2 waves 4 years	No	Physician-report	Composite from z-scores: • Memory • Attention/executive • Abstract reasoning • Visuo-constructional • Speed	No association	Age, sex, education, estimated IQ
Fischer 2009 Canada (46)	Population-based n=465 dementia-free Aged 53-90	2 waves 3 years	No	Self-report Medication use	Composite from z-scores: • Semantic memory • Fluency • Semantic speed • Speed/executive function	No association	Systolic blood pressure
Maggi 2009 Italy (30)	Population-based n=3037 dementia-free Aged $\geq 65$	3 waves 8 years	No	Self-report Medication use Medical records FBG $\geq 140$ mg/dl	MMSE (global cognition) Single cognitive tests: • Immediate/delayed recall (memory) • Attentional matrix	Greater memory decline (only in women)	Age, education

Okereke 2008 USA (20)	Population-based n=12 233 dementia-free Aged ≥65	PHS-II: 2 waves 2 years  WHS: 3 waves 4 years	No	Self-report	TICS (global cognition) Single cognitive tests: • Immediate and delayed recall; TICS-recall (memory) • Category fluency  Composite from z-scores: Global cognition Memory	Greater decline in global cognition and memory	Age, education, VRF, blood pressure, physical activity, cholesterol, depression, postmenopausal hormone use
van den Berg 2006 Netherlands (33)	Population-based n=596 Aged 85-90	5 waves 5 year	No	Medical records Medication use	MMSE (global cognition) Single cognitive tests: • Immediate/delayed recall (memory) • Stroop test (attention/executive) • Letter Digit Coding (speed)	No association	Sex, education
Arvanitakis 2004 USA (58)	Population-based n=824 dementia-free Aged ≥55	5.5 evaluations 1-9 years	No	Self-reported Medication use	Composite from factorial analysis: Episodic memory Semantic memory Working memory Visuospatial ability Perceptual speed	Faster decline in speed	Age, sex, education, stroke
Kanaya 2004 USA (48)	Population-based n=999 Aged 42-89	2 waves 4 years	OGTT 140-199 mg/dL	Self-reported FBG ≥126 mg/dL OGTT ≥200 mg/dL	MMSE (Global cognition) Single cognitive tests: • Verbal fluency • Trail Making Test-B (executive)	Greater decline in verbal fluency  No association for prediabetes	Age, education, depressive symptoms, baseline cognition, APOE ε4, estrogens

Hassing 2004 Sweden (50)	Population-based n 274 dementia-free Aged ≥80	4 waves 6 years	No	Medical records FBG ≥6.7 mmol/L	MMSE (Global cognition) Single cognitive tests: • Prose recall; Thurstone; Memory-in-reality (episodic memory) • Digit span (short-term memory) • Information; Verbal meaning (semantic memory) • Block design (visuospatial) • Digit Symbol Substitution; Figure similarity (speed)	Faster decline in MMSE, semantic memory, visuospatial, speed	Age, sex, education
Yaffe 2004 USA, Canada (41)	Population-based n=7027 women Aged >60	2 waves 4 years	FBG 6.1-7.0 mmol/L	Self-reported Medication use FBG ≥7.0 mmol/L	Single cognitive tests: • Word list recall (episodic memory) • Word fluency (verbal) • Trail Making Test-A, B (attention/executive) Composite z-score for global cognition	Faster decline in semantic memory, attention/executive  No association for prediabetes	Age, education, race, depression
Wu 2003 USA (47)	Population-based n=1789 Aged ≥60	2 waves 2 years	No	Self-reported Medication use FBG ≥126 mg/dL	Short-MMSE (global) Immediate/delayed recall (episodic memory)	No association	Age, sex, education, acculturation, hypertension, depressive symptoms
Stewart 2003 UK (183)	Population-based n=290 Aged 55-75	2 waves 3 years	No	Self-reported	Single cognitive tests: • Orientation • Immediate/delayed recall; recognition (memory) • Trail Making Test-A (speed/attention)	Increased odds of global decline	Age, sex, education, occupation, exercise, hypertension

Knopman 2001 USA (184)	Population-based n=10 936 Aged 47-70	2 waves 6 years	No	Self-reported Medication use FBG $\geq$ 126 mg/dL no-FBG $\geq$ 200 mg/dL	Single cognitive tests: • Delayed recall (memory) • DSST (speed) • Word fluency (verbal)	Greater decline in speed and verbal	Age, sex, education, centre, CNS medications use at visit 2
Fontbonne 2001 France (36)	Population-based n=961 with MMSE>26 Aged 59-71	3 waves 4 years	FBG 6.1-7.0 mmol/L	Self-reported FBG $\geq$ 7.0 mmol/L	MMSE (global cognition) Single cognitive tests: • Immediate recall; Benton Visual Retention (memory) • Trail Making Test-B; PASAT (attention/executive) • Facial Recognition (visuospatial/attention) • Raven's Matrices (Reasoning) • DSST; Finger Tapping (speed)	No association for diabetes or prediabetes	Age, sex, education
Gregg 2000 USA (185)	Population-based n=9679 women Aged $\geq$ 65	3 waves 6 years		Self-reported Insulin use	MMSE (global cognition) Single cognitive tests: • DSST (speed) • Trail Making Test-B (executive)	Greater decline in speed and executive function	Age, education, VRF, hypertension, stroke, visual impairment, estrogens use, depression

Abbreviations: APOE  $\epsilon$ 4, apolipoprotein E gene- $\epsilon$ 4 allele; BMI, body mass index; CNS, central nervous system; CVD, cardio- and cerebrovascular disorders; DSST, digit symbol substitution; FBG, fasting blood glucose; GP, general practitioner; HbA1c, glycated hemoglobin; IQ, intelligence quotient; mmol/L, millimoles per liter; MMSE, Mini-Mental State Examination; OGTT, oral glucose tolerance test; PASAT, Paced Auditory Serial Addition Test; RBG, random blood glucose; TICS, Telephone Interview for Cognitive Status; VRF, vascular risk factors.

### 11.3 SUMMARY OF THE LONGITUDINAL STUDIES ON THE ASSOCIATION BETWEEN PRE/DIABETES AND BRAIN MRI MARKERS

Reference	Study population	Follow-up	Prediabetes	Diabetes	MRI markers	Results (longitudinal)	Covariates
Shaw 2017 Australia (80)	Population-based n=322 Aged 60-66	3 waves 12 years	FBG 6.1-6.9 mmol/L	Self-reported medication use FBG $\geq 7.0$ mmol/L	1.5 Tesla Cortical thickness (CT)	High FBG (pre/diabetes) was associated with faster annual decline in CT	ICV, age, sex, education, BMI, hypertension, <i>APOE</i> $\epsilon 4$ , depression
Reitz 2016 USA (83)	Population-based n=618 dementia-free Aged $\geq 65$	2 waves 4 years	HbA1c 5.7-6.4%	Self-reported Medication use HbA1C $\geq 6.5\%$	1.5 Tesla GMV, WMV, HV, WMHV, Infarcts	No additional changes	ICV, age, sex, race, education, smoking, BMI, hypertension, HDL, <i>APOE</i> $\epsilon 4$
Kooistra 2013 Netherlands (81)	Clinical-based n=663 with atherosclerotic dis. Aged 18-79	2 waves 3.9 years	No	Self-reported Medication use RBG $\geq 11.1$ mmol/l	1.5 Tesla TBV, GMV, WMV, CSFV, VV, white matter lesions, Infarcts	Faster VV increase, Higher risk of infarcts	Age, sex, smoking, alcohol, BMI, SBP, DBP, hyperlipidemia, cerebrovascular disease
Espeland 2013 USA (multisite) (84)	Clinical trial-based n= 1366 women aged 56-80	2 waves 4.7 years	No	Self-reported Medication use FBG $>126$ mg/dL (when available)	1.5 Tesla GMV, WMV, VV, CSFV, region of interest volume	No additional changes	ICV, age, center, treatment assignment, time between scans, baseline volume
van Elderen 2010 Netherlands (82)	Clinical trial-based n=527 dementia-free with atherosclerotic dis. Aged 70-82	2 waves 3 years	No	History of diabetes FBG $\geq 7.0$ mmol/L	1.5 Tesla TBV, WMHV (periventricular & deep), Infarcts	Faster decrease TBV	Age, sex, hypertension, pravastatin treatment, and baseline TBV (longitudinal)
de Bresser 2010 Netherlands (85)	Clinical-based n=83 aged 56 to 80	2 waves 4 years	No	GP-based	1.5 Tesla TBV, CSFV, lateral VV, WMHV	Greater lateral VV increase	ICV, age, sex

Abbreviations: *APOE*  $\epsilon 4$ , apolipoprotein E gene- $\epsilon 4$  allele; BMI, body mass index; CSFV, cerebrospinal fluid volume; CT, cortical thickness; DBP, diastolic blood pressure; FBG, fasting blood glucose; GMV, grey matter volume; GP, general practitioner; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HV, hippocampal volume; ICV, intracranial volume; mmol/L, millimoles per liter; RBG, random blood glucose; SBP, systolic blood pressure; TBTV, total brain tissue volume; VV, ventricular volume; WMHV, white matter hyperintensities volume; WMV, white matter volume.

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## 11.3 DISSERTATIONS FROM THE AGING RESEARCH CENTER AND STOCKHOLM GERONTOLOGY RESEARCH CENTER, 1991-2018

### 1991

**Herlitz Agneta.** Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

### 1992

**Borell Lena.** The activity life of persons with a dementia disease.

### 1993

**Fratiglioni Laura.** Epidemiology of Alzheimer's disease. Issues of etiology and validity.

**Almkvist Ove.** Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

**Basun Hans.** Biological markers in Alzheimer's disease. Diagnostic implications.

### 1994

**Grafström Margareta.** The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

**Holmén Karin.** Loneliness among elderly - Implications for those with cognitive impairment.

**Josephsson Staffan.** Everyday activities as meeting-places in dementia.

**Stigsdotter-Neely Anna.** Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

**Forsell Yvonne.** Depression and dementia in the elderly.

### 1995

**Mattiasson Anne-Cathrine.** Autonomy in nursing home settings.

**Grut Michaela.** Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

### 1996

**Wahlin Åke.** Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

**Wills Philippa.** Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

**Lipinska Terzis Beata.** Memory and knowledge in mild Alzheimer's disease.

### 1997

**Larsson Maria.** Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

**Almberg Britt.** Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

### 1998

**Agüero-Eklund Hedda.** Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

**Guo Zhenchao.** Blood pressure and dementia in the very old. An epidemiologic study.

**Björk Hassing Linda.** Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

**Hillerås Pernilla.** Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

**1999**

**Almberg Britt.** Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

**Robins Wahlin Tarja-Brita.** Cognitive functioning in late senescence. Influences of age and health.

**Zhu Li.** Cerebrovascular disease and dementia. A population-based study.

**2000**

**Hillerås Pernilla.** Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

**von Strauss Eva.** Being old in our society: Health, functional status, and effects of research.

**2001**

**Jansson Wallis.** Family-based dementia care. Experiences from the perspective of spouses and adult children.

**Kabir Nahar Zarina.** The emerging elderly population in Bangladesh: Aspects of their health and social situation.

**Wang Hui-Xin.** The impact of lifestyles on the occurrence of dementia.

**2002**

**Fahlander Kjell.** Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

**Giron Maria Stella.** The rational use of drugs in a population of very old persons.

**2003**

**Jönsson Linus.** Economic evaluation of treatments for Alzheimer's disease.

**2004**

**Berger Anna-Karin.** Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

**Cornelius Christel.** Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

**Qiu Chengxuan.** The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

**Palmer Katie.** Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

**Larsson Kristina.** According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

**2005**

**Derwinger Anna.** Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

**De Ronchi Diana.** Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

**Passare Galina.** Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

**Jones Sari.** Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

**Karp Anita.** Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

**Nilsson Jan.** Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

**2006**

**Klarin Inga.** Drug use in the elderly – are quantity and quality compatible.

**Nilsson Erik.** Diabetes and cognitive functioning: The role of age and comorbidity.

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**Ngandu Tiia.** Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

**Jonsson Laukka Erika.** Cognitive functioning during the transition from normal aging to dementia.

## **2007**

**Ferdous Tamanna.** Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

**Westerbotn Margareta.** Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

**Rehnman Jenny.** The role of gender in face recognition. (Stockholm University)

**Nordberg Gunilla.** Formal and informal care in an urban and a rural population. Who? When? What?

**Beckman Gyllenstrand Anna.** Medication management and patient compliance in old age.

## **2008**

**Gavazzeni Joachim.** Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

**Marengoni Alessandra.** Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

**Rovio Suvi.** The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

**Xu Weili.** Diabetes mellitus and the risk of dementia. A population-based study.

**Meinow Bettina.** Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

**Agahi Neda.** Leisure in late life. Patterns of participation and relationship with health.

**Haider Syed Imran.** Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

## **2009**

**Thilers Petra.** The association between steroid hormones and cognitive performance in adulthood.

**Masud Rana AKM.** The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

**Paillard-Borg Stéphanie.** Leisure activities at old age and their influence on dementia development.

**Livner Åsa:** Prospective and retrospective memory in normal and pathological aging.

**Atti Anna-Rita.** The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

## **2010**

**Fors Stefan.** Blood on the tracks. Life-course perspectives on health inequalities in later life.

**Keller Lina.** Genetics in dementia. Impact in sequence variations for families and populations.

## **2011**

**Schön Pär.** Gender matter. Differences and changes in disability and health among our oldest women and men.

**Caracciolo Barbara.** Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

**Rieckmann Anna.** Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

## **2012**

**Haasum Ylva.** Drug use in institutionalized and home-dwelling elderly persons.

**Mangialasche Francesca.** Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

**Lovén Johanna.** Mechanism of women's own-gender bias and sex differences in memory for faces.



**2013**

**Hooshmand Babak.** The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

**Rizzuto Debora.** Living longer than expected: protective and risk factors related to human longevity.

**2014**

**Sjölund Britt-Marie.** Physical functioning in old age: Temporal trends and geographical variation in Sweden.

**Wastesson Jonas.** Unequal drug treatment: age and educational differences among older adults.

**2015**

**Sköldunger Anders.** Dementia and use of drugs: Economic modelling and population-based studies.

**Craftman Åsa Gransjön.** Medicine management in municipal home care; delegating, administrating and receiving.

**Swärd Joakim.** Emotional facial processing in younger and older adults.

**Wang Rui.** Cardiovascular risk factors, brain structure, and cognitive decline in old age.

**Pantzar Alexandra.** Cognitive performance in old-age depression.

**2016**

**Kelfve Susanne.** Gotta survey somebody: methodological challenges in population surveys of older people.

**Heap Josephine.** Living conditions in old age: Coexisting disadvantages across life domains.

**Håkansson Krister.** The role of socio-emotional factors for cognitive health in later life.

**Shakersain Behnaz.** Impact of nutritional status and diet on cognitive decline and survival.

**Bellander Martin.** Plasticity of memory functioning: genetic predictors and brain changes.

**2017**

**Ferencz Beata.** Genetic and lifestyle influences on memory, brain structure, and dementia.

**Köhncke Ylva.** Lifestyle, cognitive aging, and brain correlates.

**Santoni Giola.** How well are we aging? Capturing the complexity of health trajectories of older adults.

**Becker Nina.** Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

**2018**

**Nilsen Charlotta.** Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

**Alexander Darin-Mattsson.** Set for life? Socioeconomic conditions, occupational complexity, and later life health.